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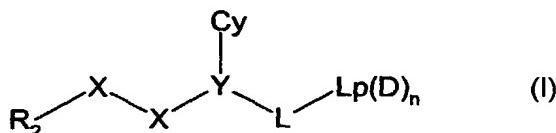
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(54) Title: COMPOUNDS



(57) Abstract: Use of compounds of formula (I) where R<sub>2</sub>, each X, L, Y, Cy, Lp, D and n are as defined in the specification, as serine protease inhibitors.

Compounds

This invention relates to compounds that are inhibitors of serine proteases. More particularly, it relates to their 5 use as serine protease inhibitors in the treatment of the human or animal body.

The serine proteases are a group of proteolytic enzymes which have a common catalytic mechanism characterized by a particularly reactive Ser residue. Examples of serine 10 proteases include trypsin, tryptase, chymotrypsin, elastase, thrombin, plasmin, kallikrein, Complement C1, acrosomal protease, lysosomal protease, cocoonase,  $\alpha$ -lytic protease, protease A, protease B, serine carboxypeptidase II, subtilisin, urokinase, Factor VIIa, Factor IXa, and Factor 15 Xa. The serine proteases have been investigated extensively over a period of several decades and the therapeutic value of inhibitors of serine proteases is well understood. (For a recent review, see, for example, Donmienne Leung et al., J. Med. Chem., Vol. 43, No. 3, 2000, pages 305-341).

Serine protease inhibitors play a central role in the regulation of a wide variety of physiological processes including coagulation, fibrinolysis, fertilization, development, malignancy, neuromuscular patterning and inflammation. It is well known that these compounds inhibit 20 a variety of circulating proteases as well as proteases that are activated or released in tissue. It is also becoming clear that serine protease inhibitors inhibit critical cellular processes, such as adhesion, migration, free radical production and apoptosis. In addition, animal 25 experiments indicate that intravenously administered serine protease inhibitors, variants or cells expressing serine 30

protease inhibitors, provide a protective effect against tissue damage.

Serine protease inhibitors have also been predicted to have potential beneficial uses in the treatment of disease 5 in a wide variety of clinical areas such as oncology, neurology, haematology, pulmonary medicine, immunology, inflammation and infectious disease.

In particular serine protease inhibitors may be beneficial in the treatment of thrombotic diseases, asthma, 10 emphysema, cirrhosis, arthritis, carcinoma, melanoma, restenosis, atheroma, trauma, shock and reperfusion injury.

Thus for example an inhibitor of Factor Xa has value as a therapeutic agent as an anticoagulant, e.g. in the treatment and prevention of thrombotic disorders. The use of 15 a Factor Xa inhibitor as an anticoagulant is desirable in view of the selectivity of its effect. Many clinically approved anticoagulants have been associated with adverse events owing to the non-specific nature of their effects on the coagulation cascade.

20 Also, there are well-known associations of  $\alpha_1$  protease inhibitor deficiency with emphysema and cirrhosis and C1 esterase inhibitor deficiency with angioedema.

25 Tryptase is the major secretory protease of human mast cells and is proposed to be involved in neuropeptide processing and tissue inflammation.

Mature human tryptase is a glycosylated, heparin-associated tetramer of catalytically active subunits. Its amino-acid structure appears to have no close counterpart among the other serine proteases which have been 30 characterised. Tryptase is stored in mast cell secretory granules and after mast cell activation, human tryptase can be measured readily in a variety of biological fluids. For

example, after anaphylaxis, tryptase appears in the blood stream where it is readily detectable for several hours.

Tryptase also appears in samples of nasal and lung lavage fluid from atopic subjects challenged with specific antigen.

5 Tryptase has been implicated in a variety of biological processes where activation and degranulation of mast cells occur. Accordingly, mast cell tryptase inhibition may be of great value in the prophylaxis and treatment of a variety of mast cell mediated conditions. Mast cells can degranulate  
10 by both IgE-dependent and independent mechanisms thereby implicating tryptase in both atopic and non-atopic inflammatory conditions. Tryptase can activate proteases such as pro-urokinase and pro-MMP3 (pro-matrix metalloprotease 3, pro-stromelysin), thereby indicating a  
15 pathological role in tissue inflammation and remodelling. Furthermore, the recent evidence that tryptase can activate certain G-protein coupled receptors (eg PAR2) and induce neurogenic inflammation points to a broader physiological role, for example in modulating pain mechanisms. Given  
20 tryptase's multiple mechanisms of action, it has been proposed that tryptase inhibitors may be beneficial in a broad range of diseases. These include conditions such as: asthma (specifically influencing the inflammatory component, the underlying hyperreactivity, and the chronic fibrotic  
25 damage due to smooth muscle thickening); chronic obstructive pulmonary disease (COPD) and pulmonary fibrotic diseases; rhinitis; psoriasis; urticaria; dermatitis; arthritis; Crohn's disease; colitis; angiogenesis; atherosclerosis; multiple sclerosis; interstitial cystitis; migraine  
30 headache; neurogenic inflammation and pain mechanisms; wound healing; cirrhosis of the liver; Kimura's disease; pre-eclampsia; bleeding problems associated with menstruation

and the menopause; cancer (particularly melanoma and tumour metastasis); pancreatitis; and certain viral infections (Yong, Exp. Toxic Pathol, 1997, 49, 409; Steinhoff et al., Nat. Med., 2000, 6, 151; Downing and Miyan, Immunol. Today, 5 2000, 21, 281; Tetlow and Wooley, Ann. Rheum. Dis., 1995, 54, 549; Jeziorska, Salamonsen and Wooley, Biol. Reprod., 1995, 53, 312; Brain, Nat. Med., 2000, 6, 134; Olness et al., Headache, 1999, 39, 101.) The underlying principle is that a tryptase inhibitor should have utility where mast 10 cells have been induced to degranulate by whatever mechanism, including anaphylactic reactions due to exogenous substances, e.g. morphine-induced bronchoconstriction (Bowman and Rand, 2<sup>nd</sup> edt., 1980.)

It has now been found that certain aromatic compounds 15 carrying lipophilic side chains are particularly effective as inhibitors of serine proteases, especially serine proteases with negatively charged P1 specificity pockets, such as factor Xa, thrombin and tryptase. Depending upon their structure, certain of these compounds have been found 20 to be selective for the serine protease, Factor Xa. Others have been found to be dual inhibitors of Factor Xa and thrombin. Yet others have been found to be selective for the serine protease, tryptase.

The Factor Xa inhibitors of this invention are 25 potentially useful for the prophylaxis or treatment of thrombotic disorders such as amongst others venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction, and cerebral thrombosis. They potentially have benefit in the treatment 30 of acute vessel closure associated with thrombolytic therapy and restenosis, e.g. after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries

and in the maintenance of vascular access patency in long term hemodialysis patients.

Factor Xa inhibitors of this invention may, with benefit, form part of a combination therapy with an 5 anticoagulant with a different mode of action or with a thrombolytic agent.

Hence, the invention also provides the use of certain compounds which have been found to be inhibitors of both Factor Xa and thrombin. These compounds have excellent 10 potential therapeutic value and may synergistically boost Fxa antithrombotic effect.

It is envisaged that the compounds that are tryptase inhibitors will be useful not only in the treatment and prophylaxis of asthma but also of other allergic and 15 inflammatory conditions mediated by tryptase such as allergic rhinitis, skin conditions such as eczema, psoriasis, atopic dermatitis and urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel disease, neurogenic inflammation, atherosclerosis and cancer.

It has been reported in WO99/11658 and WO99/11657 that 20 certain benzamidine and aminoisoquinoline derivatives carrying a bulky lipophilic side chain are excellent inhibitors of serine proteases. Unfortunately, it has since been found that benzamidine compounds of WO 99/11658 in 25 general demonstrate poor oral bioavailability.

Surprisingly, it has now been found that certain other aromatic compounds also show inhibitory activity against serine proteases, in particular Factor Xa, despite the lack 30 of the amidino or 1-aminoisoquinoline functionality previously believed to be crucial for activity as a factor Xa inhibitor, thrombin or tryptase. Many of these compounds also possess structural features in addition to the aromatic

group or properties (such as activity as tryptase inhibitors) that further distinguish them from the compounds of WO99/11658 and WO99/11657.

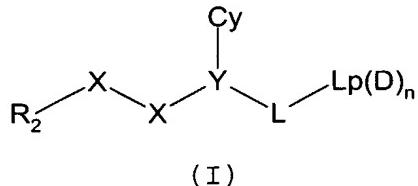
Where compounds of the invention have been tested, they 5 have generally demonstrated superior oral bioavailability in comparison with benzamidines disclosed in WO 99/11658. Also, it has been found that Factor Xa inhibitor compounds of the invention perform excellently in the prothrombin time assay (PT) when compared to aminoisoquinolines of similar Factor 10 Xa activity and structure. The PT assay is a coagulation assay and it is widely accepted that direct acting Factor Xa inhibitors which perform well in the PT assay are more likely to be good antithrombotics.

In WO99/09053 certain 2-aminobenzamide compounds are 15 disclosed as potential motilin receptor antagonists and in US 3268513 similar 2-aminobenzamide compounds are suggested as potential antibacterial agents. However, the novel compounds of the present invention have not before been suggested as potential serine protease inhibitors.

20 In WO96/09297, WO95/32945, WO94/20527 and US 5,525,623 a variety of peptide based compounds are suggested as potential inhibitors of the mast cell protease tryptase. In WO95/03333 a tryptase inhibitor is provided by a polypeptide obtainable from the leech *hirudo medicinalis*. In WO96/08275 25 secretory leukocyte protease inhibitor (SLPI) and active fragments thereof have been found to inhibit the proteolytic activity of tryptase. In WO99/55661 certain 4-aminomethylbenzoic ester derivatives are proposed as potential tryptase inhibitors.

30 Thus viewed from an one aspect the invention provides a method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a

condition responsive to a serine protease inhibitor, said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I)



where  $\text{R}_2$  represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position (in relation to the point of attachment of  $\text{X}-\text{X}$ ) by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2-$  or  $\text{R}_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or  $\text{R}_{1j}$ , and optionally substituted in the position alpha to the  $\text{X}-\text{X}$  group (i.e. 6 position for a six membered aromatic ring etc) by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, hydroxyalkyl, alkoxy or alkylthio with the proviso that  $\text{R}_2$  cannot be aminoisoquinolyl;

each  $\text{X}$  independently is a C, N, O or S atom or a CO, CR<sub>1a</sub>, C(R<sub>1a</sub>)<sub>2</sub> or NR<sub>1a</sub> group, at least one  $\text{X}$  being C, CO, CR<sub>1a</sub> or C(R<sub>1a</sub>)<sub>2</sub>;

each R<sub>1a</sub> independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino,

acyloxy methoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or 5 cyclic group;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R<sub>3a</sub> or 10 phenyl optionally substituted by R<sub>3a</sub>;

each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, 15 oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group;

D is a hydrogen bond donor group; and n is 0, 1 or 2; and

20 R<sub>1</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>, or a physiologically tolerable salt thereof, e.g. a halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

As used herein, the term "treatment" includes 25 prophylaxis, amelioration or elimination of a condition for which a human or non-human animal body is being treated.

The "effective amount" or dosage of the inhibitor compound of formula (I) will depend upon the nature and severity of the condition being treated, the administration 30 route and the size and species of the patient. However in general, quantities of from 0.01 to 100  $\mu$ mol/kg bodyweight will be administered.

Viewed from a further aspect the invention provides the use of a serine protease inhibitor compound of formula I as defined hereinabove, or physiologically tolerable salt thereof, for the manufacture of a medicament for use in a 5 method of treatment of the human or non-human animal body (e.g. a mammalian, avian or reptilian body) to combat (i.e. treat or prevent) a condition responsive to said inhibitor.

The serine protease is preferably a serine protease with a negatively charged P1 specificity pocket (i.e. 10 trypsin-like).

It has further been found that compounds of formula (I) in which R<sub>1</sub> is an unsubstituted aminoalkyl group, are selective inhibitors of tryptase. Compounds of formula (I) in which R<sub>1</sub> represents other than an unsubstituted 15 aminoalkyl group have been found to be selective inhibitors of Factor Xa, or selective dual inhibitors of Factor Xa and thrombin.

According to another aspect, therefore, the present invention provides a method of treatment of the human or 20 non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a Factor Xa inhibitor (e.g. a condition such as a thrombotic disorder, including venous thrombosis, pulmonary embolism, arterial thrombosis, myocardial ischaemia, myocardial infarction and 25 cerebral thrombosis, acute vessel closure associated with thrombolytic therapy and restenosis, including after transluminal coronary angioplasty or bypass grafting of the coronary or peripheral arteries and in the maintenance of vascular access patency in long term hemodialysis patients), 30 said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I) as defined hereinabove, provided that R<sub>1</sub> is not

an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof.

According to another aspect, therefore, the present invention provides a method of treatment of the human or 5 non-human animal body (e.g. a mammalian, avian or reptilian body) to combat a condition responsive to a tryptase inhibitor (e.g. a condition such as asthma, allergic rhinitis, eczema, psoriasis, atopic dermatitis, urticaria, rheumatoid arthritis, conjunctivitis, inflammatory bowel 10 disease, neurogenic inflammation, atherosclerosis or cancer), said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I) as defined hereinabove which is substituted in the 3 and/or 4 position by R<sub>1</sub> and in which R<sub>1</sub> is an 15 unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof.

The present invention further provides the use of a serine protease inhibitor compound of formula (I) as defined hereinabove, provided that R<sub>1</sub> is not an unsubstituted 20 aminoalkyl group, or a physiologically tolerable salt thereof for the manufacture of a medicament for use as a Factor Xa inhibitor.

The present invention further provides the use of a serine protease inhibitor compound of formula (I) as defined 25 hereinabove, which is substituted in the 3 and/or 4 position by R<sub>1</sub> and in which R<sub>1</sub> is an unsubstituted aminoalkyl group, or a physiologically tolerable salt thereof for the manufacture of a medicament for use as a tryptase inhibitor.

In the compounds of formula (I), where the alpha atom 30 is carbon it preferably has the conformation that would result from construction from a D- $\alpha$ -aminoacid NH<sub>2</sub>-CR<sub>1b</sub>(Cy)-COOH where the NH<sub>2</sub> represents part of X-X.

Likewise the fourth substituent R<sub>1b</sub> at an alpha carbon is preferably a methyl or hydroxymethyl group or hydrogen.

In the compounds of formula (I), unless otherwise indicated, aryl groups preferably contain 5 to 10 ring atoms 5 optionally including 1, 2 or 3 heteroatoms selected from O, N and S; alkyl, alkenyl or alkynyl groups or alkylene moieties preferably contain up to 6 carbons, e.g. C<sub>1-6</sub> or C<sub>1-3</sub>; cyclic groups preferably have ring sizes of 3 to 8 atoms; and fused multicyclic groups preferably contain 8 to 10 16 ring atoms.

Examples of particular values for R<sub>1a</sub> are: hydrogen, methyl or ethyl. R<sub>1a</sub> is preferably a hydrogen atom.

The linker group from the R<sub>2</sub> group to the alpha atom is preferably selected from -CH=CH-, -CONH-, -CONR<sub>1a</sub>-, -NH-CO-, 15 -NH-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-, -CH<sub>2</sub>O-, -OCH<sub>2</sub>-, -COO-, -OC=O- and -CH<sub>2</sub>CH<sub>2</sub>- . Preferably, the X moiety nearest to the alpha atom is an NH or O atom, most preferably a NH group. The X moiety alpha to the aromatic ring is preferably a carbon based group such as CH<sub>2</sub> or CO, preferably CO. Thus a 20 particularly preferred linker X-X is -CONH-. In an alternative embodiment the linker is preferably a -OCH<sub>2</sub>- group.

Examples of particular values for R<sub>1b</sub> are: hydrogen, (1-4C)alkyl, such as methyl or hydroxy(1-4C)alkyl, such as 25 hydroxymethyl. R<sub>1b</sub> is preferably a hydrogen atom.

The alpha atom (Y) is preferably a CH or C(CH<sub>3</sub>) group, especially CH.

The linker group from the alpha atom to the lipophilic group is preferably CO, CH<sub>2</sub>NH, CONR<sub>1d</sub>(CH<sub>2</sub>)<sub>m</sub>, 30 (CH<sub>2</sub>)<sub>m</sub>N(R<sub>1d</sub>)CO(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m+2</sub>, CO(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m</sub>CO, (CH<sub>2</sub>)<sub>m</sub>OC=O, (CH<sub>2</sub>)<sub>m</sub>O, CH=CH(CH<sub>2</sub>)<sub>m</sub>, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>1d</sub>, SO<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>,

$(CH_2)_mSO_2$  or  $(CH_2)_mSO_2NR_{1d}$  (where each m is independently 0 or 1 and R<sub>1d</sub> is as defined for R<sub>1a</sub>).

- Examples of particular values for R<sub>1d</sub> are: hydrogen; for alkyl optionally substituted by hydroxy, alkylamino, 5 alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as methyl or ethyl, or aryl(1-6C)alkyl, such as benzyl or phenylethyl; for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (2-6C)carboxamido, such as carboxamidomethyl; 10 for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)carboxyalkyl, such as carboxymethyl, carboxyethyl or carboxypropyl; for alkoxyalkyl optionally substituted by hydroxy, 15 alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-5C)alkoxycarbonyl(1-6C)alkyl, such as methoxycarbonylmethyl, methoxycarbonylethyl, methoxycarbonylpropyl, ethoxycarbonylmethyl, ethoxycarbonylethyl and ethoxycarbonylpropyl.

20 R<sub>1d</sub> is preferably a hydrogen atom.

The linker may be optionally branched, for example, to incorporate a polar functionality.

Examples of particular values for L are CO, CONH, CH<sub>2</sub>NHCO and CONHCH<sub>2</sub>.

25 It will be appreciated by those skilled in the art that a diverse range of organic groups are lipophilic, and that it is therefore impractical to define with precision each and every structure that may be incorporated into a serine protease inhibitor compound of formula (I). Accordingly, it 30 is being assumed that the addressee of this specification will not require an exhaustive computer listing of structures of lipophilic groups, but will instead make use

of the structures of lipophilic groups disclosed in the specification, especially those exemplified; the test systems described herein for identifying serine protease inhibitors; and common general knowledge of the 5 lipophilicity, synthesis and stability of organic compounds, to obtain novel serine protease inhibitor compounds of formula (I).

The lipophilic group may be, for example, an alkyl, alkenyl, carbocyclic or heterocyclic group, or a combination 10 of two or more such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO<sub>2</sub>, CONR<sub>1e</sub>, NR<sub>1e</sub>-CO-, NR<sub>1e</sub> linkage (where R<sub>1e</sub> is as defined for R<sub>1a</sub>), optionally substituted by one or more oxo or R<sub>3</sub> groups in which R<sub>3</sub> is alkylaminocarbonyl, alkoxy carbonylamino, N- 15 alkylaminoalkanoyl, N-alkanoylaminoalkanoyl, C-hydroxyaminoalkanoyl or as defined for R<sub>3a</sub>.

By way of illustration, representative lipophilic groups include methylcyclohexyl, methylcyclohexylmethyl, 20 methylphenylmethyl, phenylethyl, benzylpiperidinyl, benzoylpiperidinyl, bis(piperidinyl) and phenylpiperazinyl.

Phenylethyl is an example of a combination of an alkyl group and a carbocyclic group linked through a single bond.

Benzylpiperidinyl is an example of a combination of an alkyl group, a carbocyclic group and a heterocyclic group 25 linked by single bonds.

Benzoylpiperidinyl is an example of a combination of a carbocyclic group and a heterocyclic group linked through C=O.

Methylcyclohexylmethyl is an example of a combination 30 of an alkyl group (methyl) and a carbocyclic group (cyclohexyl) linked by a single bond and having a substituent R<sub>3</sub> (methyl) on cyclohexyl. It will be

appreciated that this group could alternatively have been regarded as a combination of two alkyl groups and a carbocyclic group. However, in order to provide clarity, in this specification any terminal alkyl group in L<sub>p</sub> will be  
5 treated as a substituent R<sub>3</sub>.

When the lipophilic group comprises an alkyl group, this may be, for example, a (1-3C) alkyl group, such as methyl, ethyl or propyl. Preferably an alkyl group is unsubstituted.

10 When the lipophilic group comprises a carbocyclic group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic hydrocarbon group containing up to 25, more preferably up to 10 carbon atoms. The carbocyclic group may thus be, for example, a cycloalkyl, polycycloalkyl,  
15 phenyl or naphthyl group, or a cycloalkyl group fused with a phenyl group.

Examples of particular values for a cycloalkyl group are (3-6C) cycloalkyl groups, such as cyclopentyl and cyclohexyl. A cycloalkyl group is preferably unsubstituted  
20 or substituted by one group R<sub>3</sub>, preferably amino or an alkyl group, such as methyl.

Examples of particular values for a polycycloalkyl group are (6-10C) polycycloalkyl groups, such as bicycloalkyl, for example decalinyl, norbornyl or adamantyl.  
25 A polycycloalkyl group is preferably unsubstituted or substituted by one, two or three R<sub>3</sub> groups, for example alkyl such as methyl. An example of a polycycloalkyl group substituted by alkyl is isopinocamphenyl.

A phenyl group is preferably unsubstituted or  
30 substituted by one or two R<sub>3</sub> groups. More preferably it is substituted by one or two R<sub>3</sub> groups.

A naphthyl group is preferably unsubstituted or substituted by one R<sub>3</sub> group.

Examples of a cycloalkyl or cycloalkenyl group fused with a phenyl group are indanyl and tetrahydronaphthyl. This 5 group is preferably unsubstituted or substituted by oxo or one or two R<sub>3</sub> groups. Examples of groups substituted by oxo are 1-oxoindan-5-yl, 1-oxo-5,6,7,8-tetrahydronaphth-5-yl and 1-oxo-5,6,7,8-tetrahydronaphth-6-yl.

When the lipophilic group comprises a heterocyclic 10 group, this may be, for example, a non-aromatic or aromatic, mono or polycyclic group containing one or two oxygen, nitrogen or sulfur atoms in the ring system, and in total up to 25, more preferably up to 10 ring system atoms.

Examples of a heterocyclic group when it is a non-15 aromatic monocyclic group are azacycloalkyl groups, such as pyrrolidinyl and piperidinyl; azacycloalkenyl groups, such as pyrrolinyl; diazacycloalkyl groups, such as piperazinyl; oxacycloalkyl groups, such as tetrahydropyranyl; and thiacycloalkyl groups, such as tetrahydrothiopyranyl. A non-20 aromatic monocyclic group preferably contains 5, 6 or 7 ring atoms and is preferably unsubstituted or substituted by one group R<sub>3</sub>, preferably alkyl, such as methyl or ethyl, or hydroxyalkyl, such as hydroxymethyl.

Examples of a heterocyclic group when it is a non-25 aromatic polycyclic group are bicyclic groups, such as azacycloalkyl fused with phenyl, for example dihydroindolyl, dihydroisoindolyl, tetrahydroquinolinyl and tetrahydroisoquinolinyl; azacycloalkyl fused with cycloalkyl, such as decahydroisoquinolyl, and tricyclic 30 groups, such as azacycloalkyl fused with indolyl, for example tetrahydropyrido[3,4-b]indole. This group is preferably unsubstituted.

Examples of a heterocyclic group when it is an aromatic monocyclic group are furyl, pyrrolyl, thienyl, imidazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, oxazolyl, oxadiazolyl (such as 1,3,4-oxadiazolyl), thiadiazolyl (such as 1,3,4-thiadiazolyl), triazinyl and thiazolyl. This group is preferably unsubstituted or substituted by one or two R<sub>3</sub> groups.

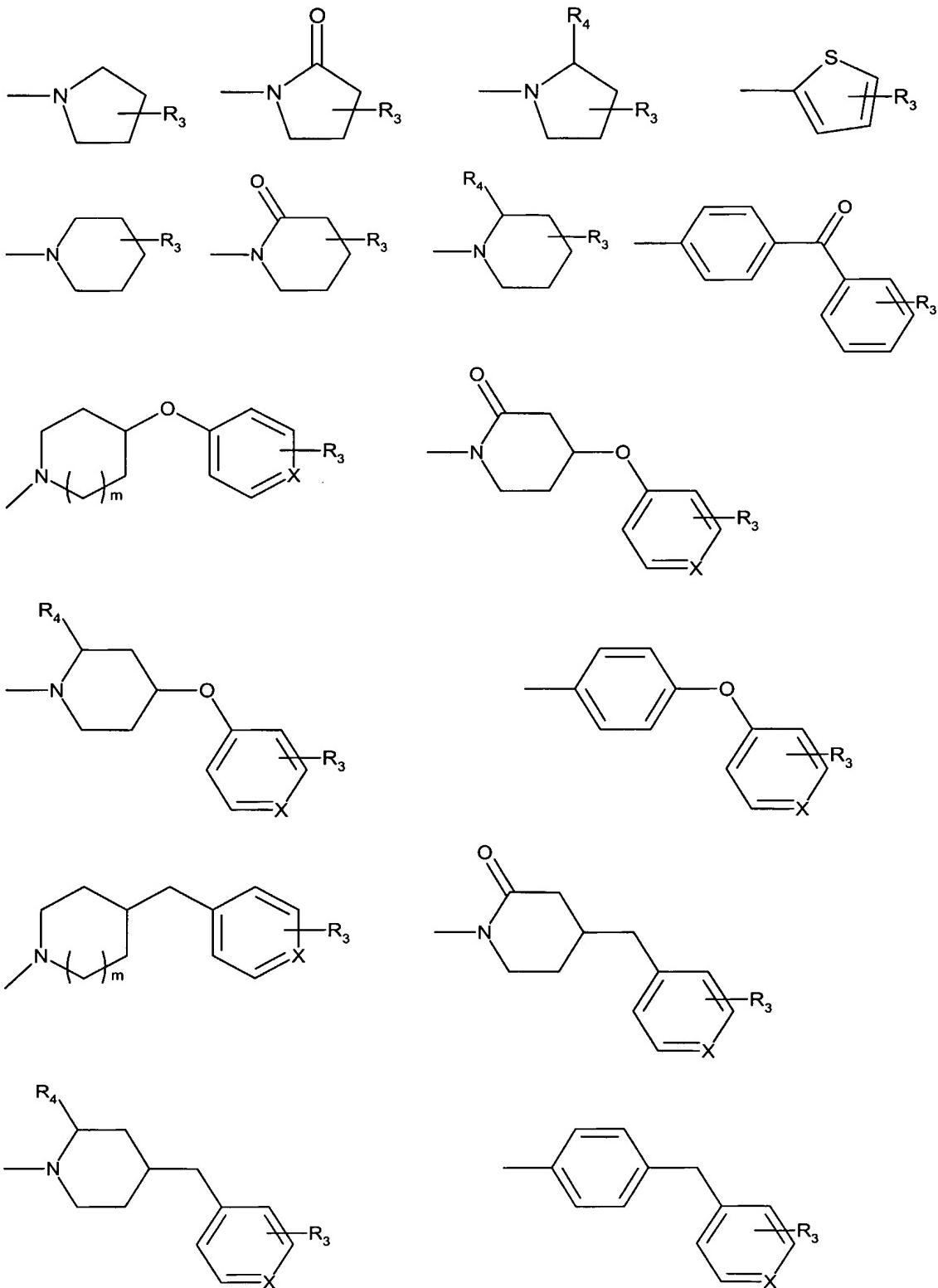
Examples of a heterocyclic group when it is an aromatic polycyclic group are bicyclic groups such as benzofuryl, quinolinyl, isoquinolinyl, benzothienyl, indolyl and benzothiazolyl. This group is preferably unsubstituted or substituted by one R<sub>3</sub>.

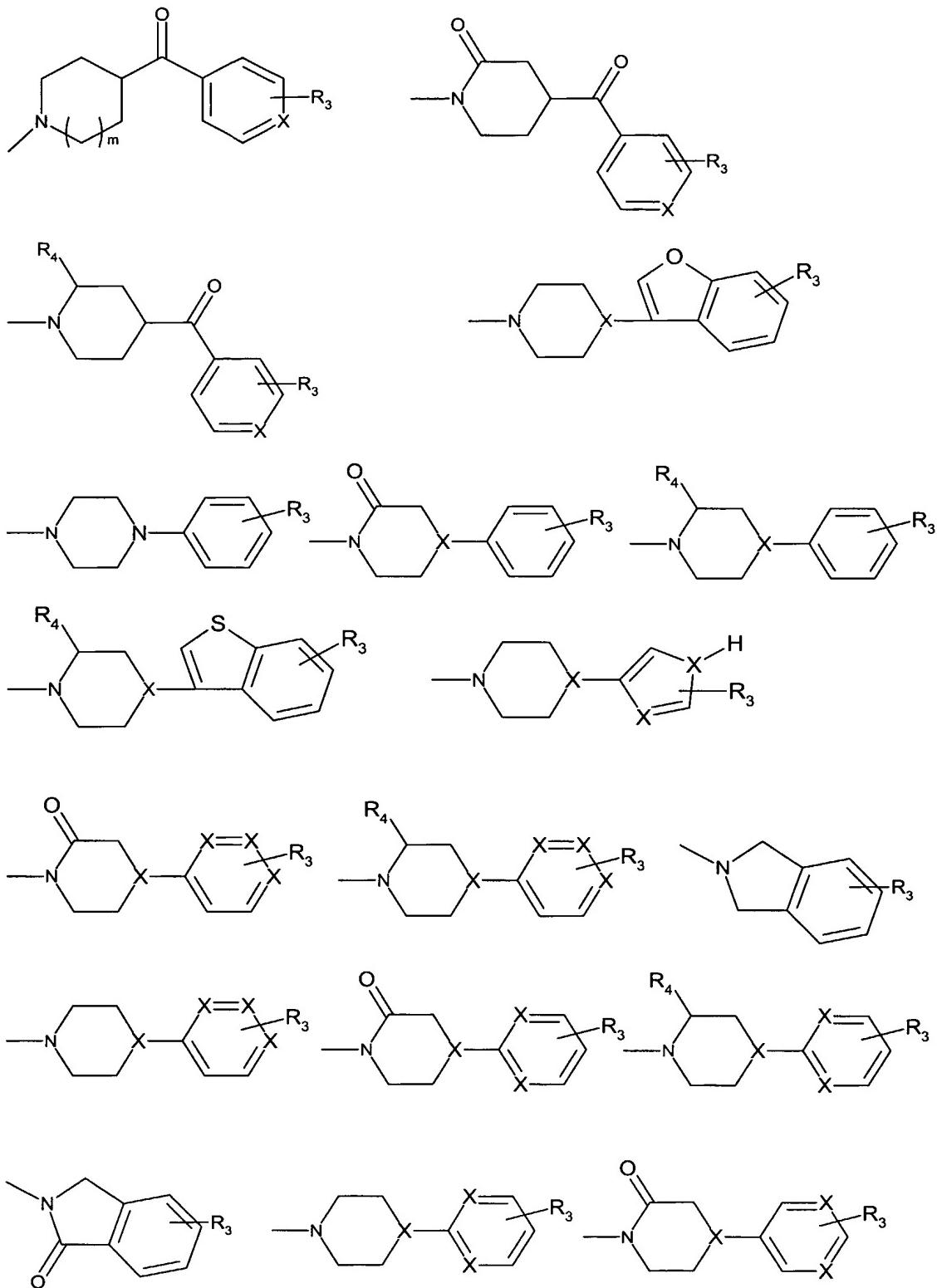
The lipophilic group preferably comprises a cycloalkyl, azacycloalkyl, diazacycloalkyl, phenyl, naphthyl, adamantyl, bicycloalkyl, mono- or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a linear or branched alkyl or alkenyl group all optionally substituted by one or more oxo or groups R<sub>3</sub>, or a combination of at least two such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO<sub>2</sub>, CONR<sub>1e</sub>, NR<sub>1e</sub>-CO- or NR<sub>1e</sub> linkage (where R<sub>1e</sub> is as defined for R<sub>1a</sub>).

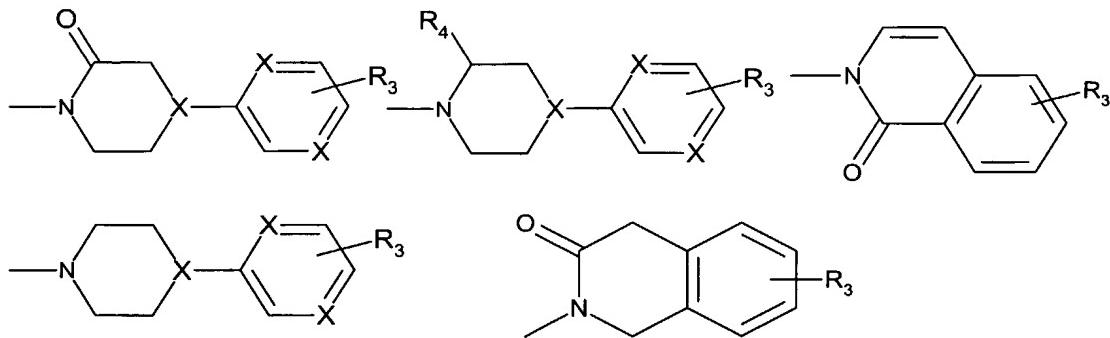
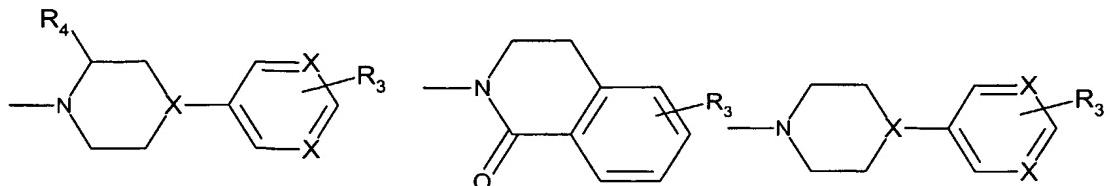
Where L<sub>p</sub> comprises a combination of at least two groups, it preferably comprises a combination of two or three such groups. The groups are preferably linked by a single bond, C=O, O or NR<sub>1e</sub>.

Examples of particular values for R<sub>1e</sub> are hydrogen and (1-6C)alkyl, such as methyl or ethyl.

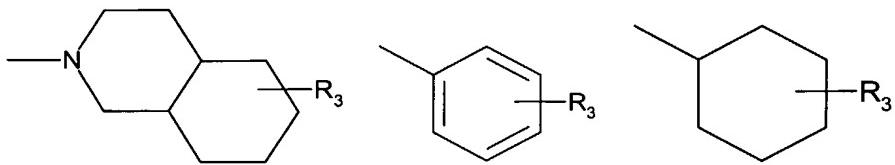
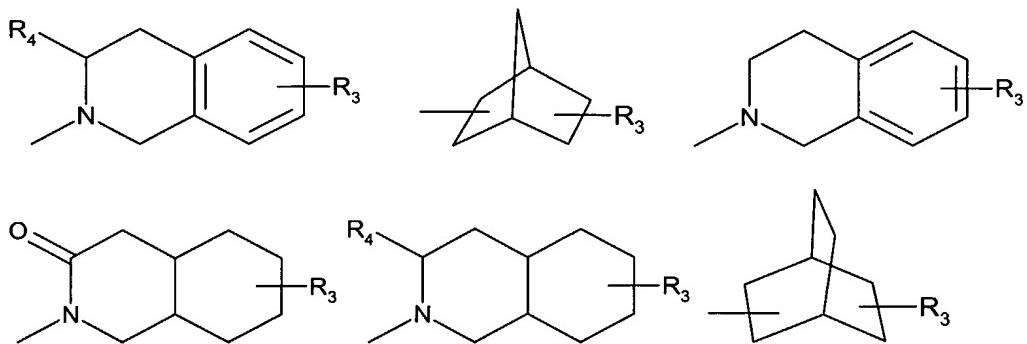
The lipophilic group L<sub>p</sub> may be selected, for example, from:





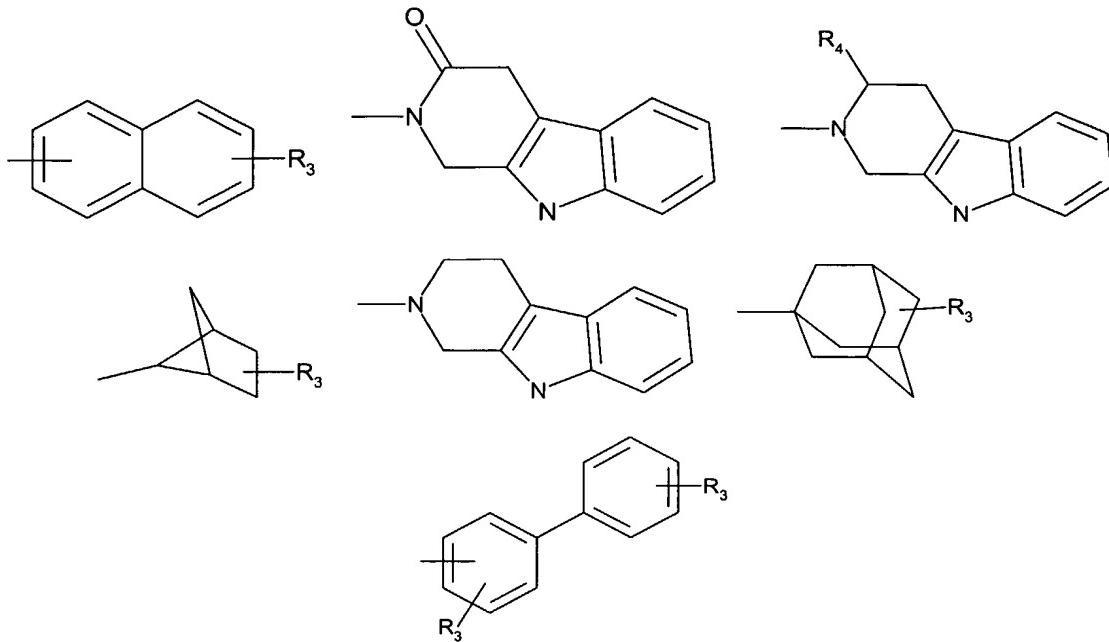


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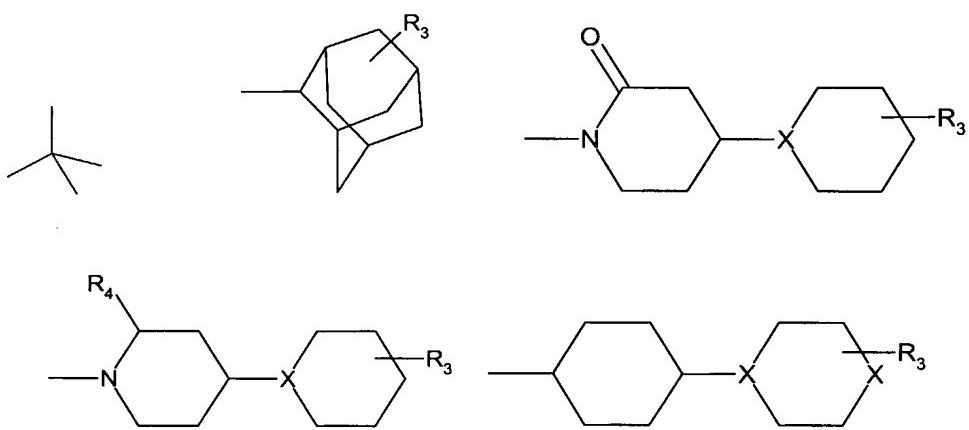


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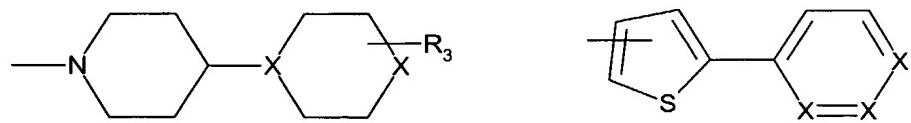
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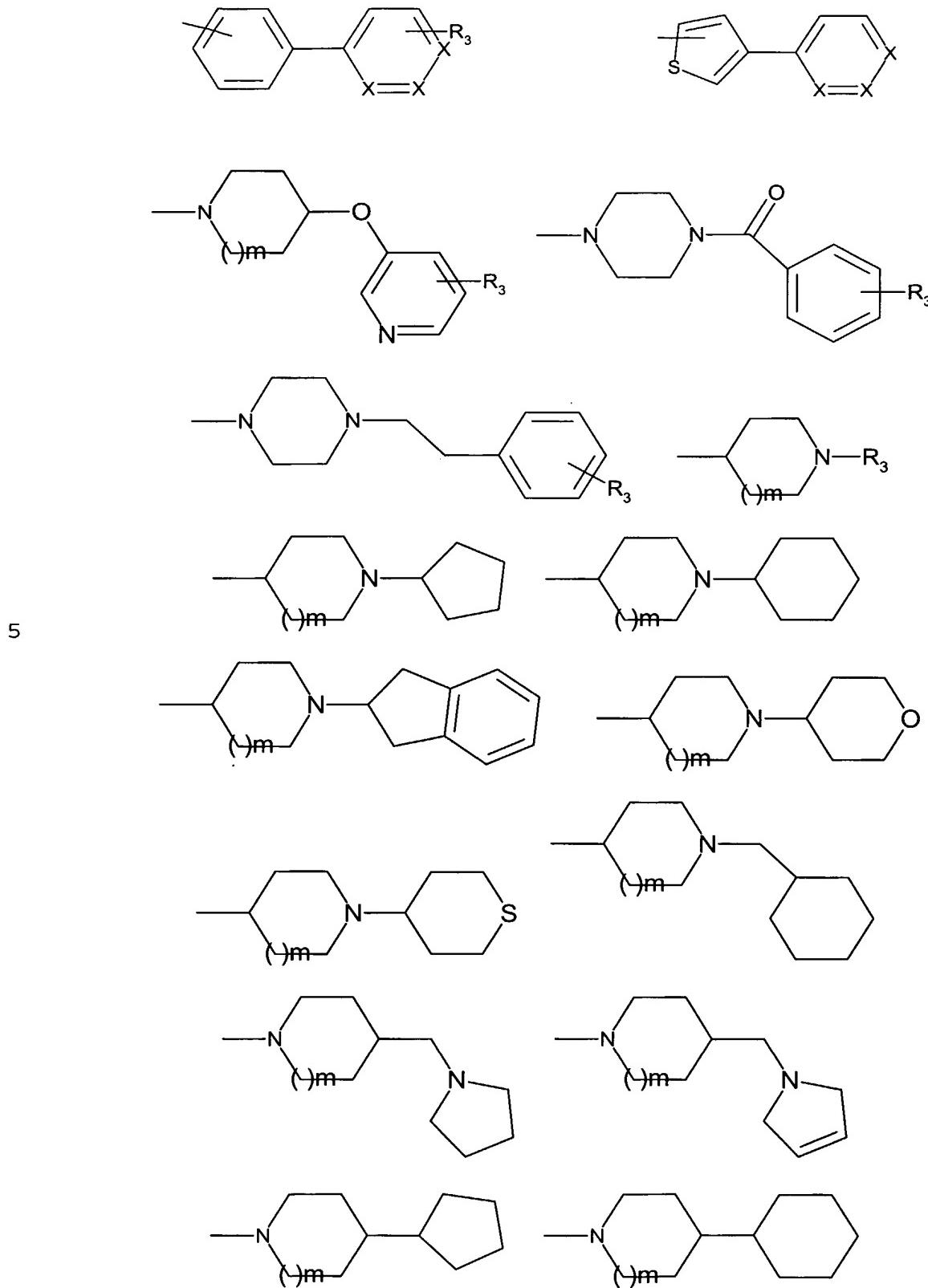


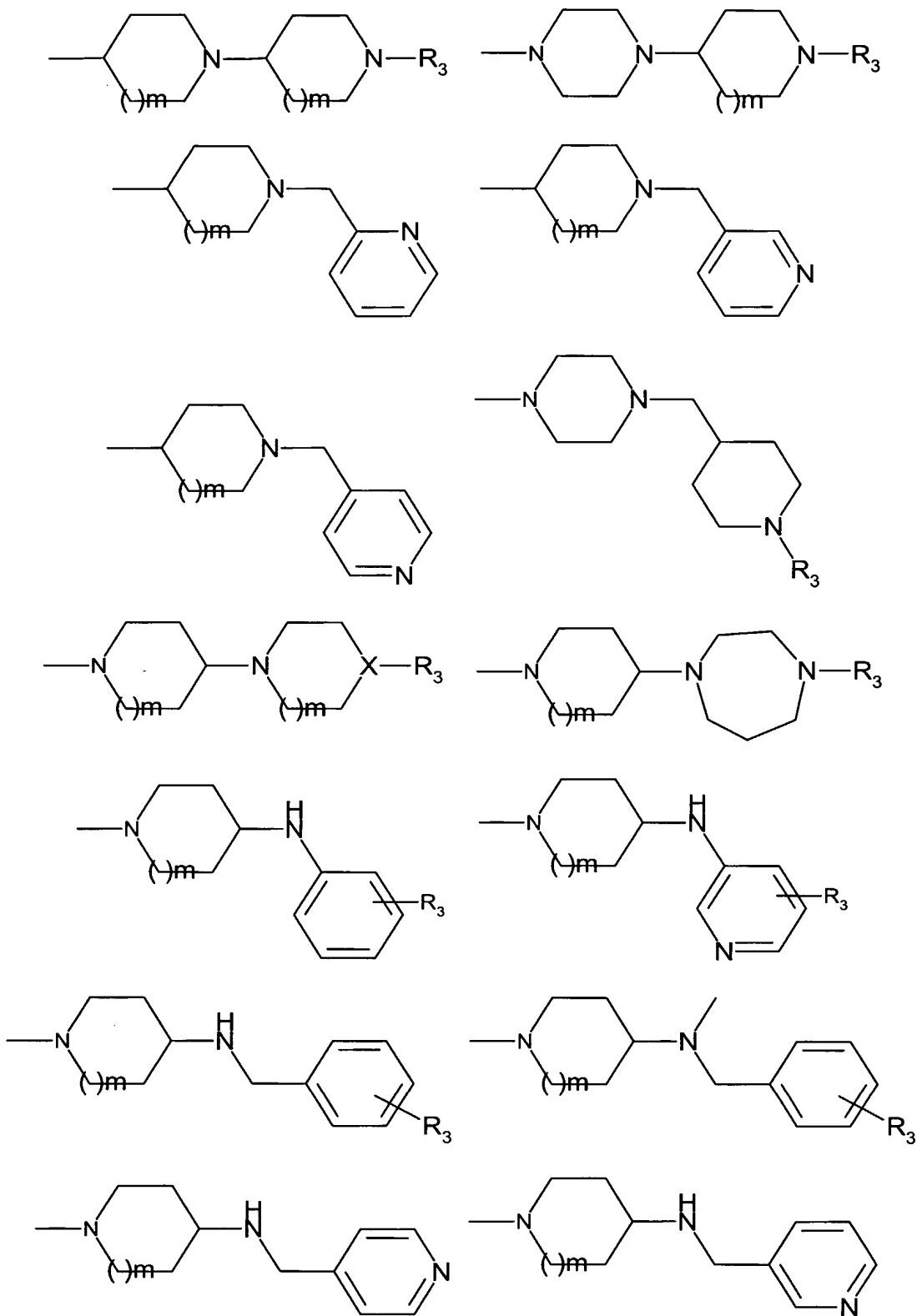
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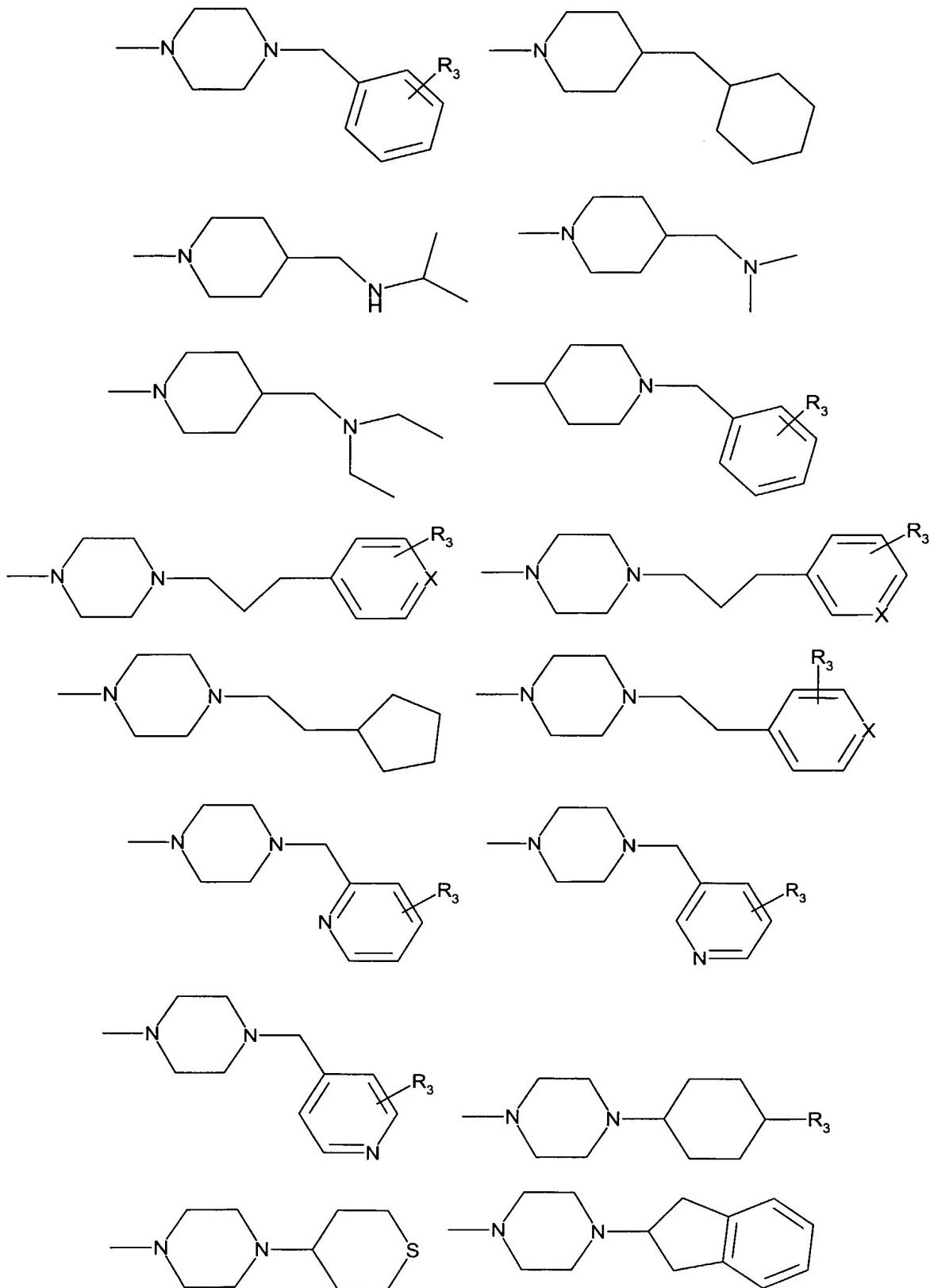


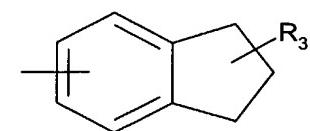
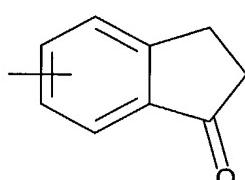
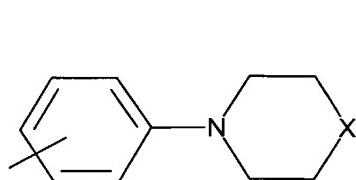
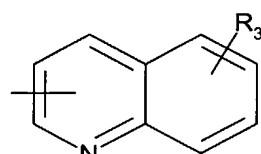
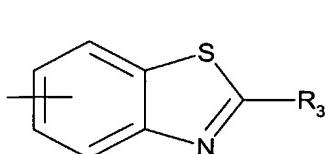
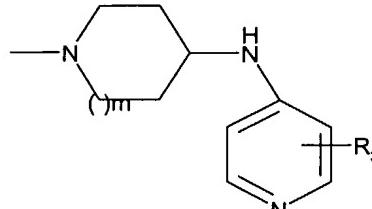
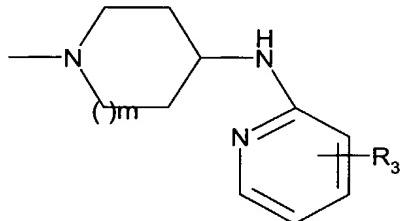
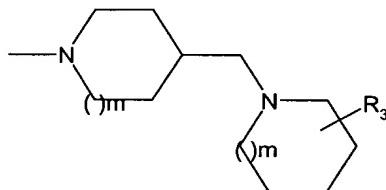
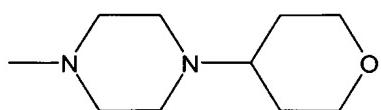
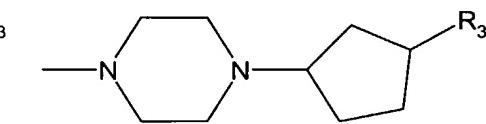
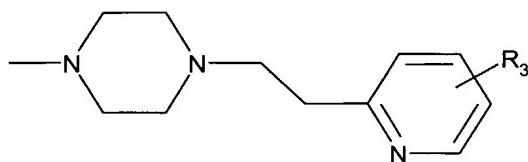
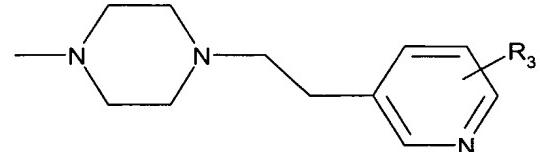
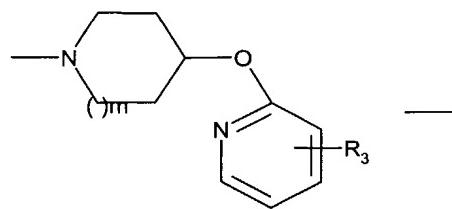
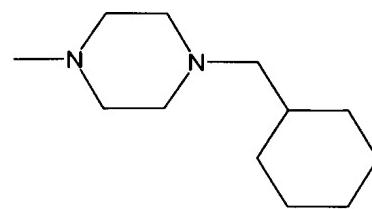
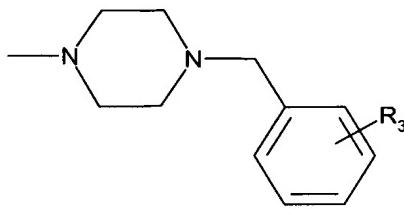
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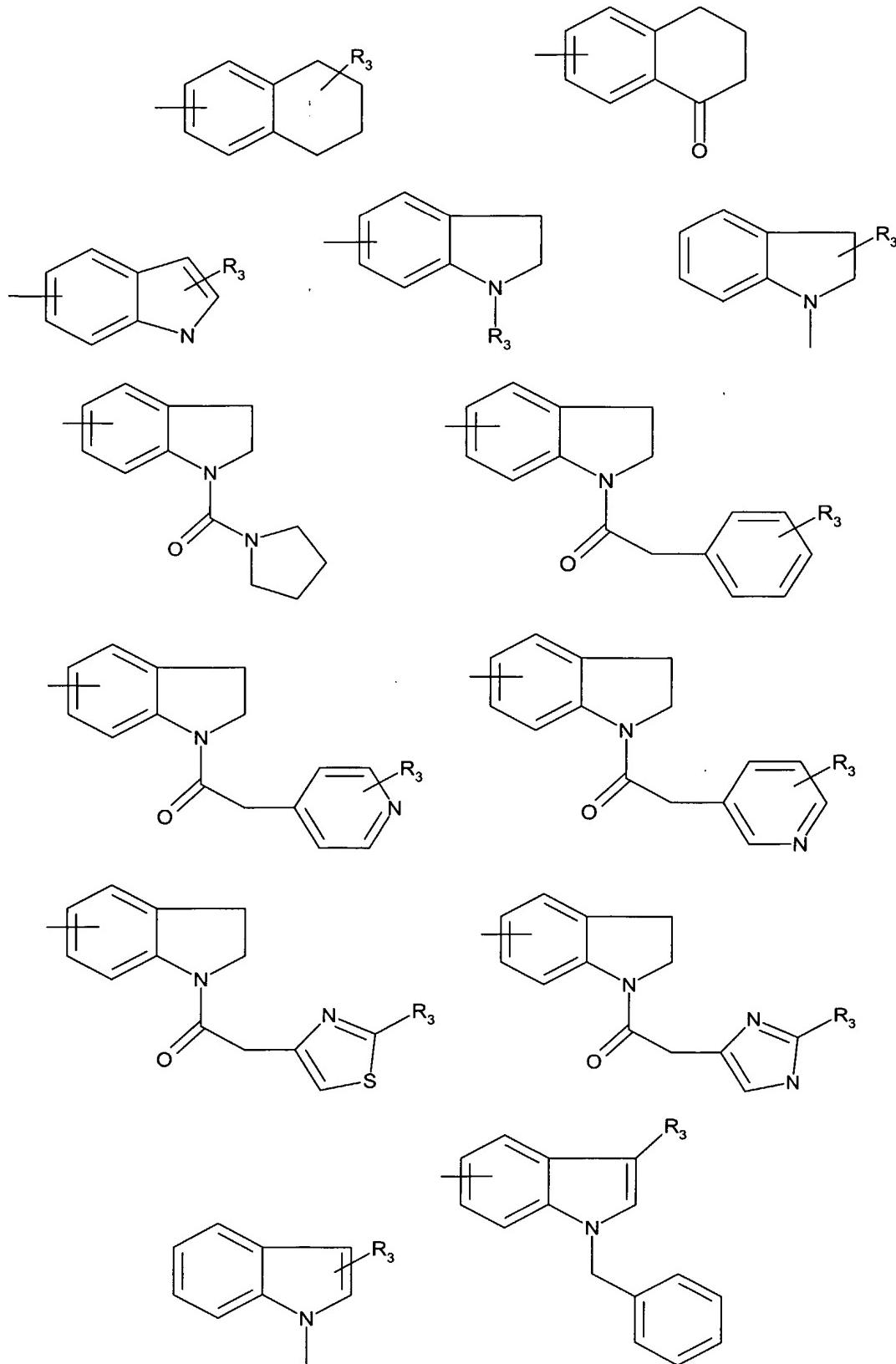












wherein R<sub>3</sub> is as hereinbefore defined;  
m represents 0 or 1;  
R<sub>4</sub> represents hydrogen, (CH<sub>2</sub>)<sub>w</sub>COOH or (CH<sub>2</sub>)<sub>w</sub>CONH<sub>2</sub>;  
5 w represents an integer from 0 to 4; and  
X represents CH or N.

Where two or more X atoms are present in a ring,  
preferably at least one is CH.

In the L<sub>p</sub> groups depicted above, preferably L  
10 represents CO when the L<sub>p</sub> group is linked to L through N, or  
CONH when the L<sub>p</sub> group is linked to L through C.

Examples of particular values for R<sub>3</sub> are:-

- for alkylaminocarbonyl: N-methyl-N-ethylaminocarbonyl,  
methylaminocarbonyl or dimethylaminocarbonyl;  
15 for N-alkylaminoalkanoyl: N-methylacetyl;  
for N-alkanoylaminoalkanoyl: 2-N-acetylaminoacetyl or 2-N-  
acetylamino propanoyl;  
for C-hydroxyaminoalkanoyl: 2-amino-3-hydroxypropanoyl or 2-  
amino-3-hydroxybutanoyl;  
20 hydrogen;  
hydroxyl;  
for alkoxy optionally substituted by hydroxy, alkylamino,  
alkoxy, oxo, aryl or cycloalkyl: alkoxy such as methoxy or  
ethoxy;  
25 for alkyl optionally substituted by hydroxy, alkylamino,  
alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkyl, such as  
methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl,  
pentyl, 2-pentyl or 3-pentyl, (1-6C)alkylamino(1-6C)alkyl,  
such as isopropylaminomethyl, dimethylamino-methyl,  
30 diethylaminomethyl or dimethylaminoethyl, or (1-6C) alkanoyl,  
such as acetyl, propionyl or isobutyryl;

for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)hydroxyalkyl, such as hydroxymethyl, or 1-hydroxyethyl or 2-hydroxyethyl, carboxy, carboxy(1-5C)alkyl or hydroxy(1-5C)alkanoyl, such as 2-hydroxyacetyl or 2-hydroxypropanoyl;

for alkoxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkoxy(1-6C)alkyl, such as methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl:

for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: amino(1-6C)alkyl such as aminomethyl, aminocarbonyl, aminocarbonyl-(1-5C)alkyl, or amino(1-6C)alkanoyl, such as aminoacetyl ( $\text{COCH}_2\text{NH}_2$ ), aminopropionyl ( $\text{COCH}_2\text{CH}_2\text{NH}_2$ ) or 2-aminopropionyl ( $\text{COCH}(\text{CH}_3)\text{NH}_2$ );

for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-6C)alkylamino such as methylamino, dimethylamino or ethylamino, or (1-6C)alkanoylamino, such as formylamino or acetylamino;

amino;

for halo: fluoro or chloro;

cyano;

nitro;

thiol;

for alkylthio: methylthio;

for alkylsulphonyl: methylsulphonyl, ethylsulphonyl or isopropylsulphonyl;

for alkylsulphenyl: methylsulphenyl;

for triazolyl: 1,2,4-triazol-2-yl, 1,2,4-triazol-4-yl or 1,2,3-triazol-4-yl;

for imidazolyl: 1,3-imidazol-1-yl or 1,3-imidazol-4-yl;

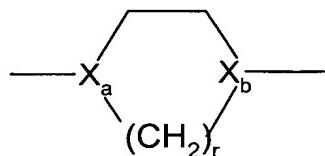
for tetrazolyl: tetrazol-1-yl or tetrazol-5-yl;  
 hydrazido;  
 for alkylsulphonamido: methylsulphonamido, ethylsulphonamido  
 or propylsulphonamido;  
 5 for alkylaminosulphonyl: methylaminosulphonyl,  
 ethylaminosulphonyl or propylaminosulphonyl;  
 aminosulphonyl;  
 for haloalkoxy: trifluoromethoxy; and  
 for haloalkyl: trifluoromethyl or trichloromethyl.

10 When R<sub>3</sub> is present as a substituent on an aromatic ring, it may be selected, for example, from hydrogen, alkylsulphonyl, aminosulphonyl, alkylaminosulphonyl, alkylaminocarbonyl, amino, amido, alkoxy carbonyl, acetyl amino, chloro, fluoro, cyano, methoxy, ethoxy, nitro, 15 hydroxy, alkylsulphonylamino, triazolyl and tetrazolyl.

When R<sub>3</sub> is present as a substituent on a saturated ring, it may be selected, for example, from hydrogen, hydroxy, amino, (1-3C)alkoxy, (1-3C)hydroxyalkyl, (1-3C)alkyl, carboxy, methoxycarbonyl and ethoxycarbonyl.

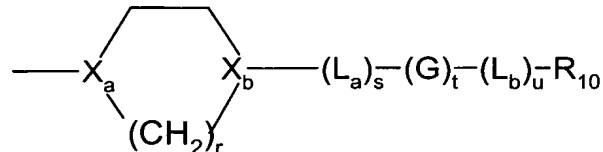
20 It has been found that certain groups L and, especially, L<sub>p</sub> are associated with selectivity for Factor Xa, whereas others are associated with selectivity for tryptase.

One group of compounds of particular interest as Factor 25 Xa inhibitors are compounds of formula (I) in which L<sub>p</sub> comprises an azacycloalkyl or diazacycloalkyl group of formula



in which r is 1 or 2, one of  $X_a$  and  $X_b$  is N and the other is CH or N, provided that when r is 1,  $X_a$  and  $X_b$  are not both N.

Preferred compounds comprising this group are those in  
5 which  $L_p$  is a group of formula:



in which:

r is 1 or 2;

one of  $X_a$  and  $X_b$  is N and the other is CH or N provided that  
10 when r is 1,  $X_a$  and  $X_b$  are not both N;

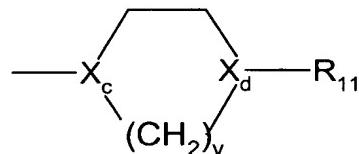
s, t and u are each 0 or 1;

$L_a$  and  $L_b$  are each independently selected from a single bond, C=O, O and NR<sub>1e</sub>, in which R<sub>1e</sub> is hydrogen or (1-6C)alkyl;

15 G is (1-6C)alkanediyl; and

R<sub>10</sub> is (1-6C)alkyl; (3-6C)cycloalkyl which is unsubstituted or substituted by (1-6C)alkyl; indanyl; pyridyl; tetrahydropyranyl; tetrahydrothiopyranyl; phenyl which is unsubstituted or substituted by one or two R<sub>3</sub> groups;

20 pyrrolinyl; or a group of formula



in which v is 1, 2 or 3; one of  $X_c$  and  $X_d$  is N and the other is CH or N, provided that when v is 1,  $X_c$  and  $X_d$  are not both N; and R<sub>11</sub> is hydrogen, (1-6C)alkyl or when  $X_d$  is CH,

25 hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when  $X_b$  is N,  $L_a$  is a bond or C=O; when  $X_c$  is N,  $L_b$  is a bond or C=O; when  $X_b$  and  $X_c$  are both N, t is 1; and

when  $(L_a)_s - (G)_t - (L_b)$  represents an alkyl group and  $X_b$  and  $X_c$  both represent N, the alkyl group contains at least two chain carbon atoms.

It will be appreciated that the provisos exclude  
5 compounds having two heteroatoms bonded directly together or separated by an alkyl group having only one carbon atom in the chain.

When  $X_a$  is N, L is preferably CO or  $CH_2CO$ .

When  $X_a$  is CH, L is preferably CONH, CONH $CH_2$  or  
10  $CH_2NHCO$ .

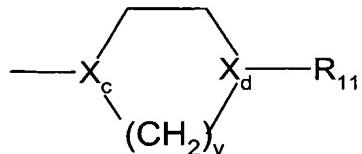
Examples of values for G are  $CH_2$ ,  $(CH_2)_2$  and  $(CH_2)_3$ .

Examples of values for  $R_{11}$  are hydrogen, methyl, ethyl or 2-propyl, or when  $X_d$  is CH, hydroxymethyl.

Examples of values for  $R_{10}$  are:

15 for (1-6C)alkyl: methyl, ethyl, 2-propyl and 3-pentyl;  
for (3-6C)cycloalkyl which is unsubstituted or substituted by (1-6C)alkyl: cyclopentyl, 3-methylcyclopentyl, cyclohexyl and 4-methylcyclohexyl;  
for indanyl: 2-indanyl;  
20 for pyridyl: pyrid-2-yl, pyrid-3-yl and pyrid-4-yl;  
for tetrahydropyranyl: tetrahydropyran-4-yl;  
for tetrahydrothiopyranyl: tetrahydrothiopyran-4-yl;  
for phenyl which is unsubstituted or substituted by one or  
two  $R_3$  groups: phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-  
25 fluorophenyl, 2-(methylthio)phenyl, 2-ethylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-methanesulphonylphenyl, 3-methanesulphonylphenyl, 4-methanesulphonylphenyl, 4-fluoro-2-methanesulphonylphenyl, 4-amino-2-methanesulphonylphenyl, 4-amido-2-  
30 methanesulphonyl-phenyl, 4-nitro-2-methanesulphonylphenyl, 2-aminosulphonylphenyl, 2-methylaminosulphonylphenyl, 2-

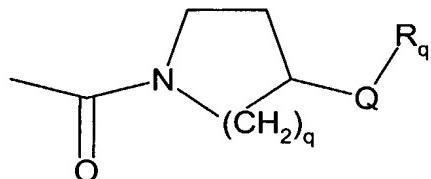
dimethylaminosulphonylphenyl, 2-methylsulphonylamino-phenyl,  
2-carboxamidophenyl and 2-acetamidophenyl;  
for pyrrolinyl: pyrrolin-1-yl; and  
for a group of formula



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piperidin-1-yl, 4-methyl-piperidin-1-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, 1-(2-propyl)piperidin-4-yl, pyrrolidin-1-yl, 3-methylpyrrolidin-1-yl, pyrrolidin-3-yl, 1-methyl-pyrrolidin-3-yl, 1-(2-propyl)pyrrolidin-3-yl, 1-methyl-piperazin-4-yl, 1-ethylpiperazin-4-yl, 1-(2-propyl)piperazin-4-yl, hexahydro-1,4-diazepin-1-yl and 4-methyl-hexahydro-1,4-diazepin-1-yl.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which



q is 1 or 2;

(a) Q is a direct bond; and R<sub>Q</sub> is piperidin-4-yl which may bear a C<sub>1-3</sub>alkyl substituent at the 1-position; or R<sub>Q</sub> is NR<sub>a</sub>R<sub>b</sub> in which each of R<sub>a</sub> and R<sub>b</sub> independently is hydrogen or C<sub>1-3</sub>alkyl; or one of R<sub>a</sub> and R<sub>b</sub> is hydrogen or methyl and the other of R<sub>a</sub> and R<sub>b</sub> is -CH<sub>2</sub>-R<sub>c</sub> or -CH<sub>2</sub>-R<sub>d</sub> in which R<sub>c</sub> is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R<sub>d</sub> is isopropyl or

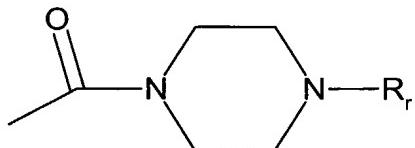
cyclopentyl, or  $\text{NR}_a\text{R}_b$  is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, 5 piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position (preferably  $\text{R}_q$  is piperidin-4-yl which may bear a (1-3C)alkyl substituent at the 1-position);

10 (b)  $\text{Q}$  is -O- or -NH-; and  $\text{R}_q$  is  $\text{R}_c$  which is defined as above ( $\text{R}_c$  is preferably pyrid-2-yl, pyrid-3-yl or pyrid-4-yl); or

(c)  $\text{Q}$  is methylene; and  $\text{R}_q$  is  $\text{NR}_a\text{R}_b$  which is defined as above.

$\text{q}$  is preferably 2.

Another group of compounds of particular interest as 15 Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)<sub>n</sub> is

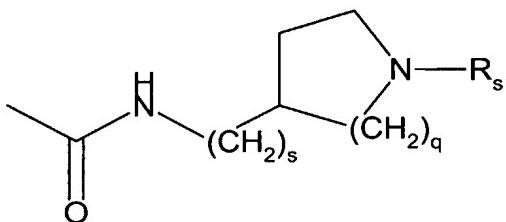


in which  $\text{R}_r$  is  $-(\text{CH}_2)_c\text{R}_c$ ,  $-\text{CHR}_e\text{R}_f$ ,  $-\text{CH}_2-\text{CHR}_e\text{R}_f$ , or  $\text{R}_g$  in which  $c$  is 1 or 2 and  $\text{R}_c$  is defined as above; each of  $\text{R}_e$  and 20  $\text{R}_f$  independently is hydrogen or C<sub>1-3</sub>alkyl; or  $\text{CHR}_e\text{R}_f$  is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4-yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), 25 piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl; and  $\text{R}_g$  is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or  $\text{R}_g$  is  $\lambda^{6-1,1-}$  dioxobenzo[b]thiophen-7-yl.

Preferably c is 2.

Preferably R<sub>c</sub> is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl.

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which  
5 -L-Lp(D)<sub>n</sub> is



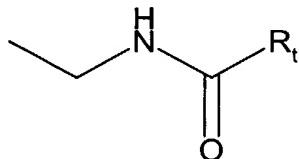
in which q is 1 or 2;

s is 0 or 1; and

R<sub>s</sub> is -(CH<sub>2</sub>)<sub>c</sub>-R<sub>C</sub>, -CHR<sub>e</sub>R<sub>f</sub>, or -CH<sub>2</sub>-CHR<sub>e</sub>R<sub>f</sub> each of which  
10 is defined as above.

Preferably s is 1.

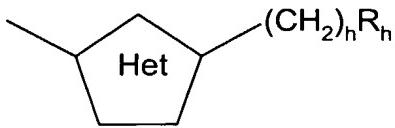
Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)<sub>n</sub> is



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in which R<sub>t</sub> is piperidin-4-yl, piperidin-3-yl or pyrrolidin-3-yl (especially piperidin-4-yl), any of which may bear a C<sub>1-3</sub> alkyl substituent at the 1-position (preferably methyl, ethyl or, more preferably, 2-propyl); or R<sub>t</sub> is phenyl (which phenyl may bear a fluoro, chloro, C<sub>1-4</sub> alkyl, methoxy or methylsulphonyl substituent).

Another group of compounds of particular interest as Factor Xa inhibitors are compounds of formula (I) in which -L-Lp(D)<sub>n</sub> is



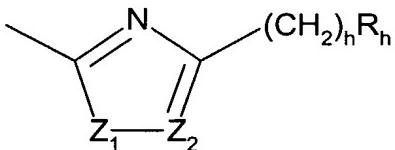
in which Het is a divalent 5 membered heteroaromatic group containing 1, 2 or 3 heteroatoms selected from O, N and S and having the two ring atoms at which it is connected

5 separated by one ring atom;

h is 0 or 1; and

R<sub>h</sub> is phenyl which may bear one or more R<sub>3</sub> substituents, for example independently selected from, for an ortho or a para substituent: C<sub>1-5</sub> alkyl, fluoro, chloro, difluoromethyl, trifluoromethyl, methoxy, dimethylamino, methylsulphonyl, and C<sub>1-2</sub> acyl, and for a meta substituent: fluoro, chloro and methyl.

Within this sub-group, a particularly preferred group of compounds is that in which -L-Lp(D)<sub>n</sub> is



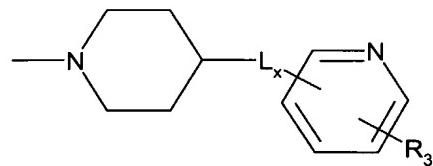
15

in which R<sub>h</sub> is phenyl which may bear one or two R<sub>3</sub> substituents, for example an ortho and/or a para substituent independently selected from, for an ortho: methyl, fluoro, chloro, methylsulphonyl and acetyl, and for a para substituent: methyl, fluoro, chloro, methoxy and dimethylamino;

Z<sub>1</sub> is S, Z<sub>2</sub> is CH, h is 0; or

Z<sub>1</sub> is NH, Z<sub>2</sub> is N, h is 1.

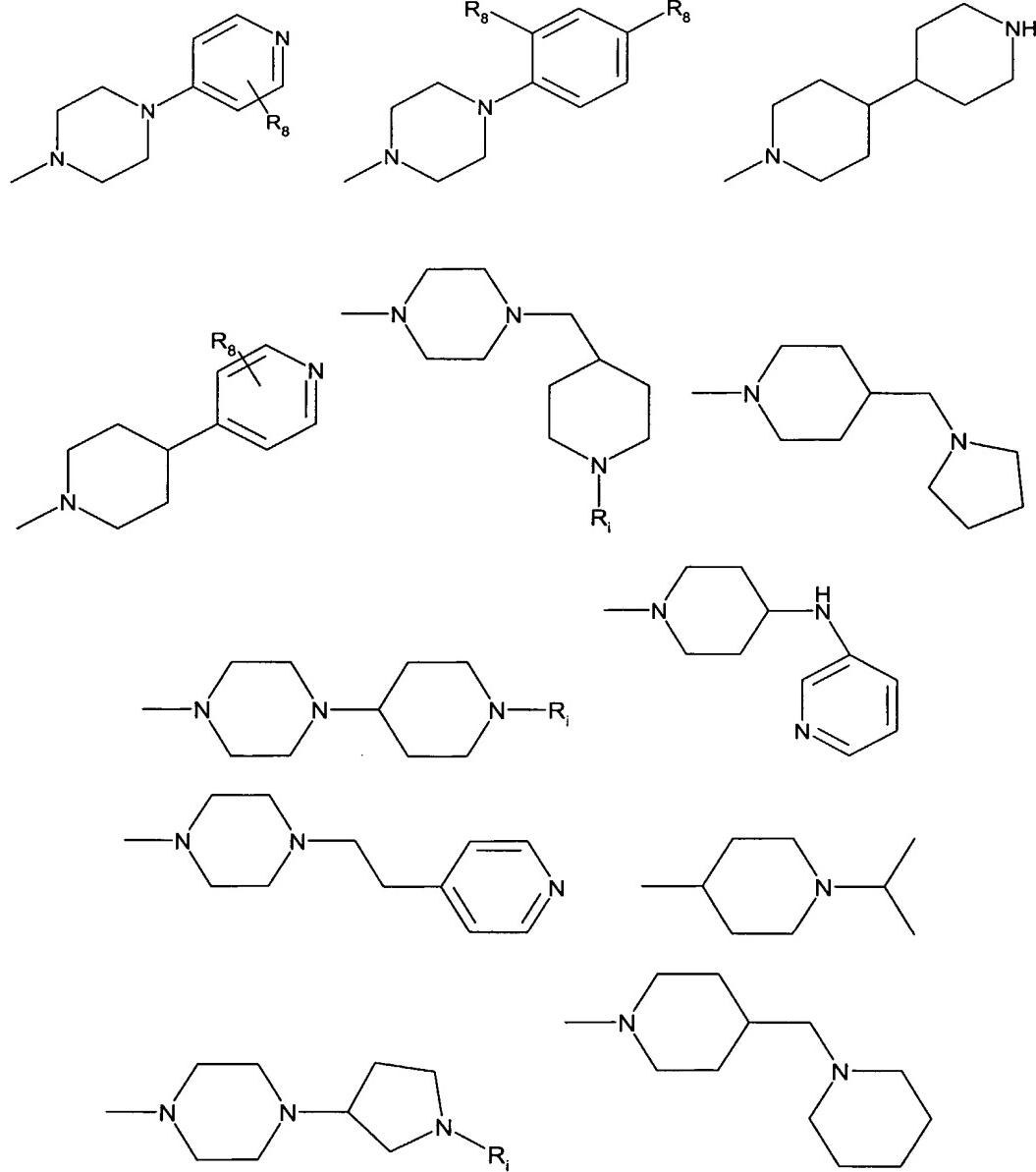
One group of lipophilic groups Lp that has been found 25 to be associated with Factor Xa inhibitor activity is that of formula



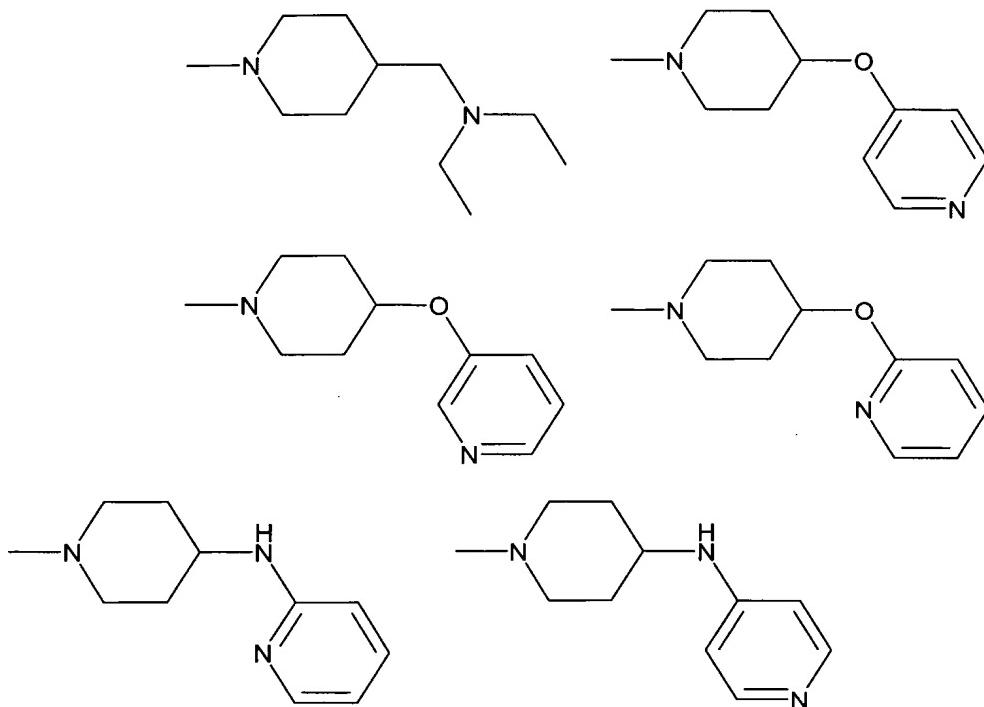
in which  $L_x$  represents O or NH.

Examples of specific lipophilic groups of interest in Factor Xa inhibitors include

5

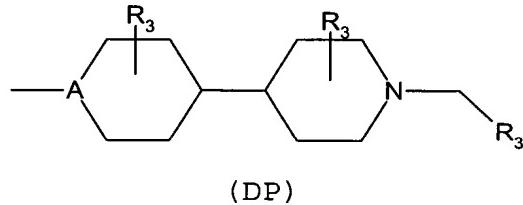


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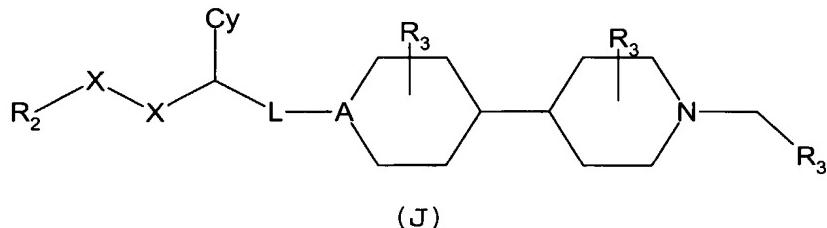
where  $R_8$  is as defined for  $R_3$  (preferably as defined for a  
5 substituent on an aromatic ring), especially where  $R_8$   
represents H, OMe,  $SO_2$ Me, F, cyano, amido, amino,  $NO_2$ , Cl or  
OH; and  $R_i$  is hydrogen or (1-6C)alkyl (such as methyl, ethyl  
or 2-propyl).

Another highly preferred lipophilic group in compounds  
10 of interest as Factor Xa inhibitors is of formula (DP)



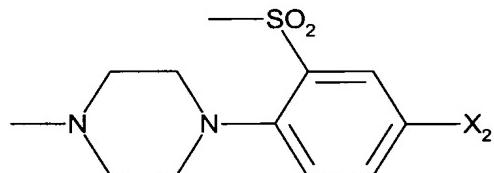
wherein A represents N or CH (preferably N) and  $R_3$  is as  
15 hereinbefore defined. When the lipophilic group is (DP) it  
is preferred that the group L represents CO,  $CH_2$  or  $SO_2$ .  
Also, it is preferred if the  $R_3$  groups in the formula DP are  
hydrogen.

Hence, preferred compounds of formula (I) for use as Factor Xa inhibitors are those of formula (J)



5 where  $R_2$ ,  $X-X$ , and  $Cy$  are as hereinbefore defined and  $L$  represents  $CO$ ,  $CH_2$  or  $SO_2$ .

Another highly preferred lipophilic group in Factor Xa inhibitors is based on the formula (K)



10 (K)

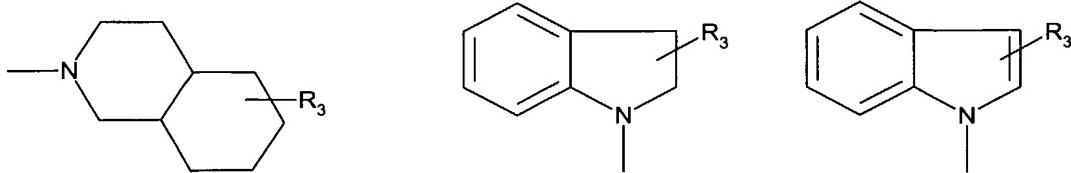
wherein  $X_2$  is halo, hydrogen, amino, nitro or  $CONH_2$ .

Preferably  $X_2$  is hydrogen or fluoro. Compounds in which the lipophilic group is based on the formula (K) or (J) have been found to perform relatively well in the prothrombin time assay, when compared with corresponding aminoisoquinolines of WO99/11657.

One group of compounds of particular interest as tryptase inhibitors is that in which  $L$  represents  $CO$  and  $L_p$  represents

20

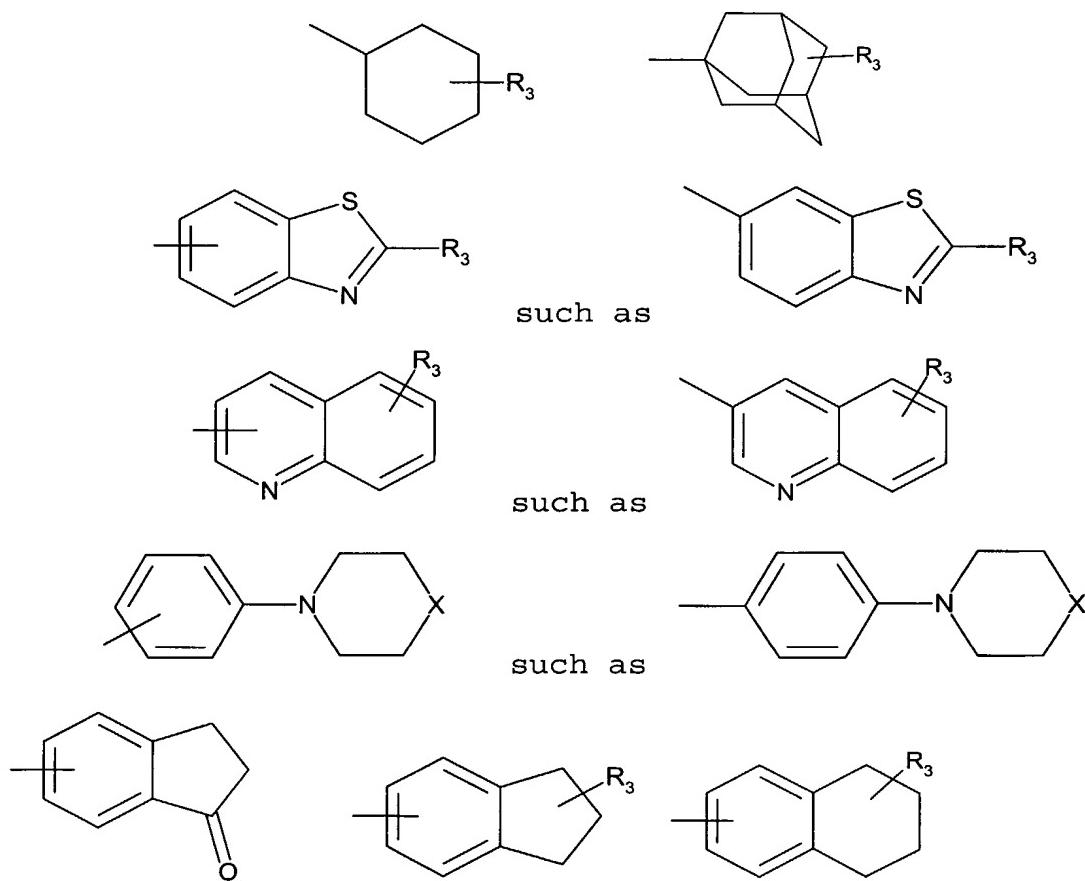


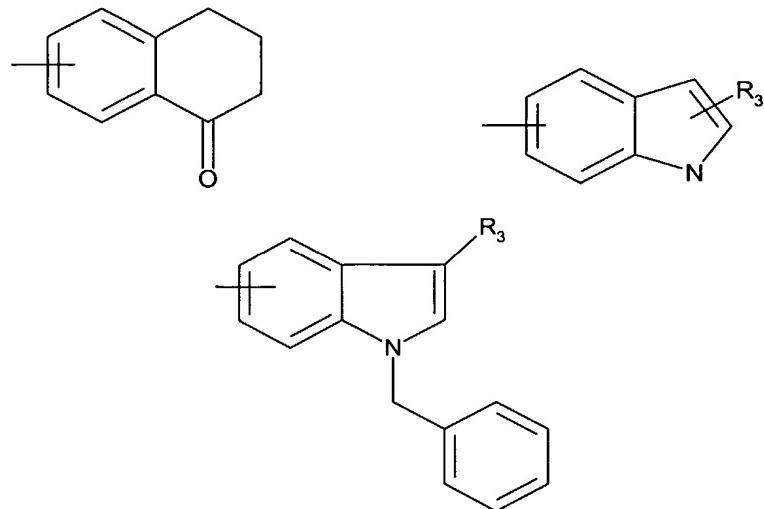


In this group of compounds, R<sub>3</sub> preferably represents hydrogen, hydroxyl or alkylaminocarbonyl.

Examples of particular values for Lp in this sub-group  
5 are pyrrolidin-1-yl, piperidin-1-yl, 3-N-methyl, N-ethyldiaminocarbonylpiperidin-1-yl, decahydroisoquinolin-2-yl and 2,3-dihydroindol-1-yl.

Another group of compounds of particular interest as  
tryptase inhibitors is that in which L represents CONH and  
10 Lp represents





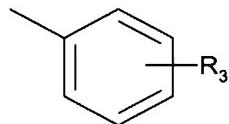
in which X is CH or N.

In this group of compounds, R<sub>3</sub> is preferably hydrogen, 5 amino, hydroxy, alkyl or aminoalkyl.

Examples of particular values are:

- (i) 2-aminocyclohexyl or 4-aminomethylcyclohexyl;
- (ii) adamantyl;
- (iii) 2-aminobenzothiazol-6-yl;
- 10 (iv) quinolin-3-yl;
- (v) 4-piperidin-1-ylphenyl or 4-piperazin-1-ylphenyl;
- (vi) 1-oxoindan-5-yl;
- (vii) indan-5-yl;
- (viii) tetrahydronaphth-6-yl or 1-methyltetrahydronaphth-6-15 yl;
- (ix) 1-oxotetrahydronaphth-6-yl or 1-oxotetrahydronaphth-7-yl;
- (x) 2,3-dimethylindol-5-yl; and
- (xi) (N-benzyl-3-acetylindol-5-yl or N-benzyl-3-acetylindol-20 7-yl).

Another group of compounds of particular interest as tryptase inhibitors is that in which L represents CONH and Lp represents

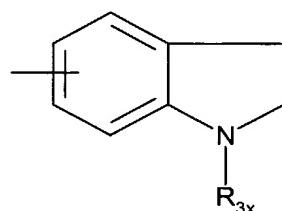


in which R<sub>3</sub> is alkylaminocarbonyl, N-alkylaminoalkanoyl, N-alkanoylaminoalkanoyl, C-hydroxyaminoalkanoyl, hydrogen, alkoxy, alkyl, aminoalkyl, aminocarbonyl, hydroxyalkyl,  
 5 alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl, alkylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido,  
 10 alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl.

Preferably the phenyl group is unsubstituted or substituted by one or two R<sub>3</sub> groups.

Examples of particular values are phenyl, 3-cyano-4-methylphenyl, 3-aminocarbonylphenyl, 4-aminocarbonyl-phenyl,  
 15 4-chloro-3-aminocarbonyl-phenyl, 4-chlorophenyl, 3,5-dichlorophenyl, 3-aminomethylphenyl, 4-methyl-3-acetylaminophenyl, 4-(1-hydroxethyl)phenyl and 4-isopropylphenyl.

20 Another particular group of compounds of formula I of interest as tryptase inhibitors is that in which L represents CONH and L<sub>p</sub> represents



in which R<sub>3x</sub> represents R<sub>3</sub> or a group of formula

25 - (CO)<sub>p</sub> - (G<sub>1</sub>) - R<sub>j</sub>

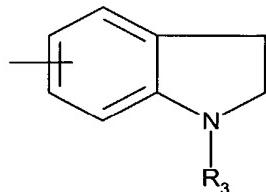
in which p is 0 or 1; G<sub>1</sub> represents (1-3C) alkanediyl or, when p is 1, a bond; and R<sub>j</sub> represents a carbocyclic or heterocyclic group, optionally substituted by R<sub>3</sub>.

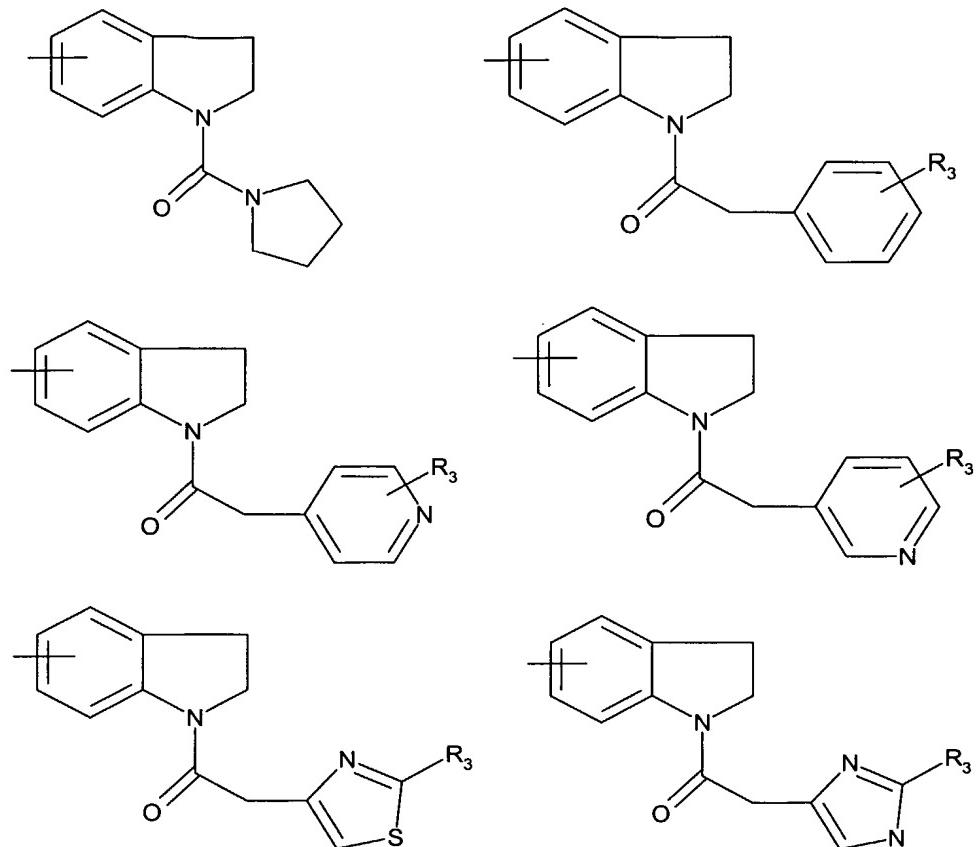
It will be appreciated that when L<sub>p</sub> represents a group as described above, it corresponds to a group in which L<sub>p</sub> is a combination of a heterocyclic group (2,3-dihydroindolyl), a carbocyclic or heterocyclic group (R<sub>j</sub>) and optionally an alkyl group (G<sub>1</sub>), which groups are linked by a single bond or a carbonyl group. Accordingly, examples of particular values for R<sub>j</sub> are the examples given above for a carbocyclic or heterocyclic group forming part of L<sub>p</sub>. Particular mention may be made of pyrrolidinyl, such as pyrrolidin-1-yl, phenyl, thiazolyl, such as thiazol-4-yl, imidazolyl, such as imidazol-4-yl, and pyridyl, such as pyrid-2-yl, pyrid-3-yl and pyrid-4-yl.

Examples of values for G are -CH<sub>2</sub>-, and CH<sub>2</sub>CH<sub>2</sub>.

The 2,3-dihydroindolyl group in the above formula is preferably a 2,3-dihydroindol-5-yl or -6-yl group, especially a 2,3-dihydroindol-6-yl group.

Examples of structures of compounds comprising a 2,3-dihydroindolyl group as described above are:





When  $R_3$  is a substituent on the 1-position of a 2,3-dihydroindolyl group, it preferably represents alkylaminocarbonyl; N-alkylaminoalkanoyl; N- alkanoylaminoalkanoyl; C-hydroxyaminoalkanoyl; hydrogen; alkyl; alkanoyl; alkoxy carbonyl; acyloxymethoxycarbonyl; aminoalkyl; aminoalkanoyl; hydroxylalkyl; hydroxylalkanoyl; alkoxyalkyl; or alkanoylamino. Examples of particular values are: N-methylaminoacetyl, N-acetylaminoacetyl, N- acetylalaninoyl, serinoyl, threoninoyl, hydrogen, methyl, acetyl, propanoyl, 2-methylpropanoyl, 3-methylbutyryl, 2-hydroxypropanoyl, hydroxylacetyl, aminoacetyl and alaninoyl.

Accordingly, examples of particular values for  $L_p$  are: 1-(N-methylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N- acetylaminoacetyl)-2,3-dihydroindol-6-yl; 1-(N- acetylalaninoyl)-2,3-dihydroindol-6-yl; 1-(serinoyl)-2,3-

dihydroindol-6-yl; 1-(threoninoyl)-2,3-dihydroindol-6-yl; 2,3-dihydroindol-5-yl; 1-methyl-2,3-dihydroindol-6-yl; 1-acetyl-2,3-dihydroindol-6-yl; 1-propanoyl-2,3-dihydroindol-6-yl; 1-(2-methylpropanoyl)-2,3-dihydroindol-6-yl; ; 1-(3-methylbutyryl)-2,3-dihydroindol-6-yl; 1-(2-hydroxpropanoyl)-2,3-dihydroindol-6-yl; 1-hydroxacetyl-2,3-dihydroindol-6-yl; 1-aminoacetyl-2,3-dihydroindol-6-yl and 1-alaninoyl-2,3-dihydroindol-6-yl.

When R<sub>3</sub> is a substituent on a phenyl, thiazolyl, imidazolyl or pyridyl group, it is preferably hydrogen, amino, alkyl or aminoalkyl. Examples of particular values are hydrogen, amino, alkyl or aminomethyl.

Accordingly, further examples of particular values for L<sub>p</sub> are: 2,3-dihydroindol-5-yl, 1-prolinoyl-2,3-dihydroindol-6-yl, 1-phenylacetyl-2,3-dihydroindol-6-yl, 1-(2-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(3-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-hydroxy)phenylacetyl-2,3-dihydroindol-6-yl, 1-(4-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-(3-pyridyl)acetyl-2,3-dihydroindol-6-yl, 1-imidazol-4-ylacetyl-2,3-dihydroindol-6-yl, 1-(2-aminothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl, and 1-(2-formamidothiazol-4-yl)acetyl-2,3-dihydroindol-6-yl.

The hydrogen bond donor group which may be attached to the lipophilic group preferably has a nitrogen or oxygen atom as the hydrogen bearing donor atom and conveniently is a hydroxyl group, a primary, secondary or tertiary amine, or a primary or secondary imine group (as part of an amidine or guanidine) or a saturated or unsaturated heterocyclic group containing a ring nitrogen, preferably a group containing 5 to 7 ring atoms. Where the donor atom is a ring nitrogen,

the remote portion of the heterocyclic ring may be part of the lipophilic group.

The cyclic group attached to the alpha carbon is preferably an optionally R<sub>3a</sub> substituted phenyl, pyridyl (such as pyrid-2-yl, pyrid-3-yl or pyrid-4-yl), thienyl (such as thien-2-yl or thien-3-yl), thiazolyl (such as thiazol-2-yl, thiazol-4-yl or thiazol-5-yl), naphthyl (such as naphth-1-yl), piperidinyl (such as piperidin-4-yl) or cycloalkyl, such as a cyclohexyl group.

- 10 Examples of particular values for R<sub>3a</sub> are:-  
hydrogen;  
hydroxyl;  
for alkoxy: methoxy or ethoxy;  
for alkyl optionally substituted by hydroxy, alkylamino,  
15 alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, or alkylaminoalkyl, such as methylaminomethyl or dimethylaminomethyl;  
for hydroxyalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: hydroxymethyl  
20 or carboxy;  
for alkoxyalkyl: methoxymethyl;  
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;  
for alkylaminocarbonyl: methylaminocarbonyl or dimethylaminocarbonyl;  
25 for aminoalkyl optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub> or aminoacetyl;  
for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-  
30 6C) alkanoylamino, such as formylamino or acetylamino;  
for alkoxycarbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino;

amino;  
for halo: fluoro or chloro;  
cyano;  
nitro;  
5 thiol;  
for alkylthio: methylthio;  
for alkylsulphonyl: methylsulphonyl or ethylsulphonyl;  
for alkylsulphenyl: methylsulphenyl;  
for imidazolyl: imidazol-4-yl;  
10 hydrazido;  
for alkylimidazolyl: 2-methylimidazol-4-yl;  
for alkylsulphonamido: methylsulphonylamido or  
ethylsulphonylamido;  
for alkylaminosulphonyl: methylaminosulphonyl or  
15 ethylaminosulphonyl;  
aminosulphonyl;  
for haloalkoxy: trifluoromethoxy; and  
for haloalkyl: trifluoromethyl.

Examples of particular values for R<sub>1C</sub> are:

20 hydrogen;  
hydroxyl;  
for alkoxy: methoxy or ethoxy;  
for alkyl optionally substituted by hydroxy, alkylamino,  
alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or  
25 ethyl, or alkylaminoalkyl, such as methylaminomethyl or  
dimethylaminomethyl;  
for hydroxyalkyl: hydroxymethyl;  
for alkoxyalkyl: methoxymethyl;  
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl;  
30 for alkylaminocarbonyl: methylaminocarbonyl or  
dimethylaminocarbonyl;

for alkoxy carbonylamino: methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino; for alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: (1-5) alkanoylamino, such as formylamino or acetyl amino; and for aminoalkyl substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl: aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub> or aminoacetyl.

Cy is preferably unsubstituted or substituted by one or  
10 two R<sub>3a</sub> groups.

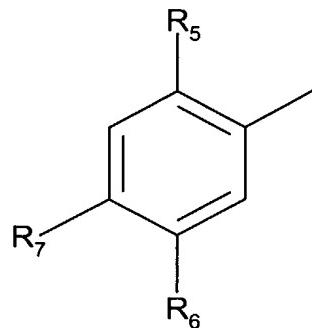
Preferably R<sub>3a</sub> is hydrogen, hydroxyl, methoxy, methyl, amino, aminomethyl, hydroxymethyl, formylamino, acetyl amino, aminoacetyl, fluoro, chloro, ethylsulphonylamino, amido or methylaminocarbonyl.

15 Examples of particular values for Cy are phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 2-hydroxymethylphenyl, 3-hydroxymethylphenyl, 4-hydroxymethylphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, 2-aminothiazol-4-yl, 2-formylaminothiazol-4-yl, 2-aminothiazol-5-yl, 2-formylaminothiazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 4-aminopyrid-3-yl, 4-aminopyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl and naphth-1-yl.

Referring to the group R<sub>2</sub>, examples of a 5 or 6  
30 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom are phenyl; pyrrolyl, such as 2-pyrrolyl; pyridyl, such as 3-pyridyl; pyrazinyl,

such as 2-pyrazinyl; furyl, such as 2-furyl; and thienyl, such as 2-thienyl or 3-thienyl. Preferably the ring is interrupted (i.e. a carbon atom is replaced) by at most one heteroatom. More preferably the ring is phenyl, 2-thienyl or 2-pyrrolyl. Most preferably, the ring is phenyl.

When the ring is phenyl, the group R<sub>2</sub> may be a group of formula



in which R<sub>5</sub> is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R<sub>6</sub> and R<sub>7</sub> which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R<sub>1</sub> or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered heterocyclic ring, which may itself be substituted by R<sub>1j</sub>, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy.

When the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring, examples of the resultant bicyclic ring are naphthyl, such as 2-naphthyl; benzimidazolyl, such as benzimidazol-5-yl or benzimidazol-6-yl; isoquinolinyl, such as isoquinolin-7-yl; indolyl, such as indol-2-yl, indol-5-yl or indol-6-yl; indazolyl, such as indazol-5-yl; indazol-6-yl; 3,4-methylenedioxophenyl; dihydroindolyl, such as 2,3-dihydroindol-6-yl; benzothiazolyl, such as benzothiazol-2-yl or benzothiazol-6-

yl; benzo[b]thiophenyl, such as benzo[b]thiophen-2-yl; benzofuryl, such as benzofur-2-yl; imidazo[1,2-a]pyrimidinyl, such as imidazo[1,2-a]pyrimidin-2-yl; tetrahydroimidazo[1,2-a]pyrimidinyl, such as 5 tetrahydroimidazo[1,2-a]pyrimidin-2-yl; and benzisoxazolyl, such as benzisoxazol-5-yl.

R<sub>2</sub> preferably represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, 10 hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, and optionally substituted at the 6 position by amino, hydroxy, 15 halo, alkyl, carboxy, alkoxy carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub> and 20 optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or 25 benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at 30 the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

5 (vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

10 (ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

15 (xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

20 (xii) indol-2-yl optionally substituted on the indole nitrogen atom by alkyl and optionally substituted at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

25 (xiii) indol-6-yl substituted at the 5 position by amino, hydroxy, halo (such as fluoro or chloro), alkyl, carboxy, alkoxy carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio and optionally substituted at the 3 position by halo (such as chloro), haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>; or

30 (xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5

or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>.

Examples of particular values for substituents that may be present on R<sub>2</sub> are:

- 5 for halo: fluoro, chloro, bromo or iodo;
- nitro;
- thiol;
- for haloalkoxy: difluoromethoxy or trifluoromethoxy;
- hydrazido;
- 10 for alkylhydrazido: methylhydrazido;
- amino;
- cyano;
- for haloalkyl: trifluoromethyl;
- for alkylthio: methylthio;
- 15 for alkenyl: vinyl;
- for alkynyl: ethynyl;
- for acylamino: acetylamino;
- carboxy;
- for acyloxy: acetoxy;
- 20 hydroxy;
- for alkyl: methyl or ethyl;
- amido (CONH<sub>2</sub>);
- for aminoalkyl: aminomethyl; and
- for alkoxy: methoxy or ethoxy.

- 25 Examples of particular values for R<sub>1</sub> are:

- hydrogen;
- hydroxy;
- for alkoxy: methoxy or ethoxy;
- for alkyl optionally substituted by hydroxy, alkylamino,
- 30 alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or ethyl, alkylaminoalkyl, such as dimethylaminomethyl, or alkanoyl, such as acetyl;

for hydroxyalkyl: hydroxymethyl;  
for alkoxyalkyl: methoxymethyl;  
for alkoxycarbonyl: methoxycarbonyl;  
for alkylaminocarbonyl: methylaminocarbonyl;  
5 for alkylamino: methylamino, ethylamino or dimethylamino;  
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy,  
oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and  
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy,  
oxo, aryl or cycloalkyl: amido ( $\text{CONH}_2$ ) or amidomethyl.

10 Examples of particular values for  $R_{1j}$  are:

hydrogen;

hydroxy;

for alkoxy: methoxy or ethoxy;

15 for alkyl optionally substituted by hydroxy, alkylamino,  
alkoxy, oxo, aryl or cycloalkyl: alkyl, such as methyl or  
ethyl, or alkanoyl, such as acetyl;

for hydroxyalkyl: hydroxymethyl;

for alkoxyalkyl: methoxymethyl;

for alkoxycarbonyl: methoxycarbonyl;

20 for alkylamino: methylamino, ethylamino or dimethylamino;  
for hydroxyalkyl substituted by hydroxy, alkylamino, alkoxy,  
oxo, aryl or cycloalkyl: carboxyl or carboxymethyl; and  
for aminoalkyl substituted by hydroxy, alkylamino, alkoxy,  
oxo, aryl or cycloalkyl: amido ( $\text{CONH}_2$ ) or amidomethyl.

25 More preferably  $R_2$  represents:

(i) phenyl optionally being substituted in the 3  
and/or 4 position by fluoro, chloro, bromo, iodo, nitro,  
difluoromethoxy, trifluoromethoxy, amino, cyano,  
trifluoromethyl, methylthio, vinyl, carboxy, acetoxy,  
30  $\text{MeSO}_2^-$ , hydroxy, methoxy, ethoxy, methyl, aminomethyl,  
methoxycarbonyl, methylamino, ethylamino or amido, and  
optionally substituted at the 6 position by amino, hydroxy,

fluoro, methoxycarbonyl, cyano or aminomethyl (preferably phenyl substituted in the 4 position by chloro, amino, vinyl, methylamino, methyl or methoxy, optionally at the 3 position with amino or hydroxy, and optionally at the 6 position with amino or hydroxy);

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl,  
10 indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy (preferably indol-6-yl optionally substituted at the 3 position by chloro, bromo, methyl or methoxy);

15 (iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

20 (vi) 3,4-methylenedioxypyhenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

25 (viii) pyrazol-2-yl substituted at the 5 position by methyl;

(ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

30 (xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

5 (xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

10 (xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy.

Examples of particular values for R<sub>2</sub> are:

(i) phenyl, 2-aminophenyl, 3-aminophenyl, 2-amino-3-fluorophenyl, 2-amino-4-fluorophenyl, 2-amino-4-chlorophenyl, 2-amino-3-bromophenyl, 2-amino-3-nitrophenyl, 15 2-amino-4-nitrophenyl, 3,4-dimethoxy-5-aminophenyl, 2-amino-4-methylphenyl, 2-amino-3-methylphenyl, 2-amino-3-methoxyphenyl, 3,4-diaminophenyl, 3,5-diaminophenyl, 3-amino-4-fluorophenyl, 3-amino-4-chlorophenyl, 3-amino-4-bromophenyl, 3-amino-4-hydroxyphenyl, 3-amino-4-carboxymethylphenyl, 3-amino-4-methylphenyl, 3-amino-4-methoxyphenyl, 2-fluorophenyl, 4-fluoro-3-cyanophenyl, 3-chlorophenyl, 3-chloro-4-hydroxyphenyl, 3-chloro-5-hydroxyphenyl, 4-chlorophenyl, 4-chloro-2-hydroxyphenyl, 4-chloro-3-hydroxyphenyl, 4-chloro-3-methylphenyl, 4-chloro-3-methoxyphenyl, 4-bromophenyl, 4-bromo-3-methylphenyl, 4-iodophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 3-cyano-5-aminophenyl, 2-hydroxyphenyl, 2-hydroxy-4-methoxyphenyl, 3-hydroxyphenyl, 3-hydroxy-4-methylphenyl, 2,4-dihydroxyphenyl, 3,4-dihydroxyphenyl, 3-hydroxy-4-methoxyphenyl, 4-difluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 4-methylthiophenyl, 4-methoxycarbonylphenyl, 4-acetoxyphenyl,

4-methanesulfonylphenyl, 3-methylphenyl, 3-aminomethylphenyl, 3-aminomethyl-6-aminophenyl, 3-methyl-5-aminophenyl, 4-methylphenyl, 4-vinylphenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 4-methoxy-3-chlorophenyl, 4-methoxy-3-methylphenyl, 3-methylaminophenyl, 4-methylaminophenyl, 4-ethylaminophenyl or 2-aminomethylphenyl;

5 (ii) naphth-2-yl, 3-aminonaphth-2-yl, 3-hydroxynaphth-2-yl or 6-hydroxynaphth-2-yl;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, 3-chloroindol-6-yl, 3-bromoindol-6-yl, 3-methylindol-6-yl, 3-methoxyindol-6-yl, indazol-5-yl, 3-aminoindazol-5-yl, indazol-6-yl, benzothiazol-6-yl, 3-aminobenzisoxazol-5-yl;

10 (iv) benzimidazol-5-yl, 2-aminobenzimidazol-5-yl, or benzothiazol-6-yl;

(v) thien-2-yl, 5-methylthien-2-yl, 5-methylthio-thien-2-yl, 5-acetylthien-2-yl or thien-3-yl;

(vi) 3,4-methylenedioxypyhenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

15 (vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) 5-methylpyrazol-2-yl;

(ix) 5-chloropyrid-2-yl;

(x) pyrid-3-yl, 6-chloropyrid-3-yl;

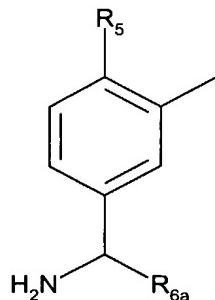
20 (xi) benzofur-2-yl, 5-chlorobenzofur-2-yl, 3-methylbenzofur-2-yl, 5-methylbenzofur-2-yl, 6-methoxybenzofur-2-yl;

(xii) indol-2-yl, 5-fluoroindol-2-yl, 5-chloroindol-2-yl, 5-methylindol-2-yl, 5-methoxindol-2-yl, 6-methoxyindol-2-yl and 1-methyl-indol-2-yl;

25 (xiii) 5-fluoroindol-6-yl; or

(xiv) benzo[b]thiophen-2-yl, 5-chlorobenzo[b]thiophen-2-yl or 6-chlorobenzo[b]thiophen-2-yl.

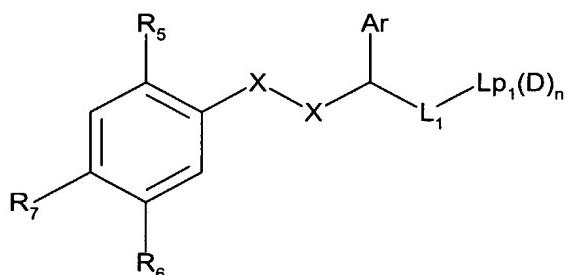
It has been found that in compounds of formula (I) that have been found to be tryptase inhibitors, the aromatic R<sub>2</sub> group is of the formula



in which R<sub>5</sub> is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and R<sub>6a</sub> is hydrogen or methyl.

For a tryptase inhibitor, preferably R<sub>2</sub> is 3-aminomethylphenyl or 3-aminomethyl-6-aminophenyl. Most preferably it is 3-aminomethylphenyl.

In one embodiment the aromatic R<sub>2</sub> group is an optionally substituted phenyl, naphthyl, indolyl or isoindolyl group and accordingly, preferred compounds of formula (I) are of formula (II)



(II)

wherein R<sub>5</sub> is amino, hydroxy or hydrogen, and R<sub>6</sub> and R<sub>7</sub> which may be the same or different represent halo, nitro, thiol, cyano, haloalkyl, haloalkoxy, amido, hydrazido, amino, alkylthio, alkenyl, alkynyl or R<sub>1</sub> or taken together form a 5 or 6 membered fused carbocyclic ring or 5 membered

heterocyclic ring, which may itself be substituted by R<sub>1j</sub>, amino, halo, cyano, nitro, thiol, alkylthio, haloalkyl, haloalkoxy;

Ar is an unsubstituted or substituted aryl group,  
5 preferably phenyl;

X-X is -CONH-, -CH<sub>2</sub>CH<sub>2</sub>-, CH<sub>2</sub>O-, -COO-, -CH<sub>2</sub>NH-, -OCH<sub>2</sub>-  
or -NHCH<sub>2</sub>-, especially -CONH-;

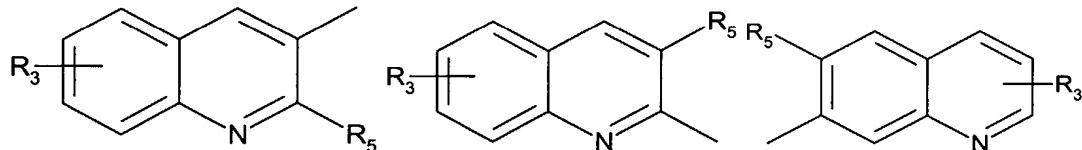
L<sub>1</sub> is a valence bond or an organic linker group  
containing 1 to 4 backbone atoms selected from C, N, O and  
10 S;

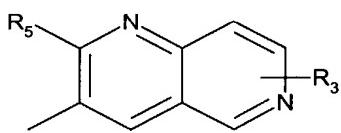
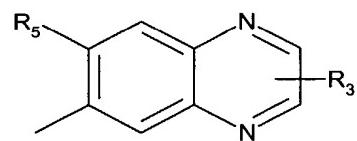
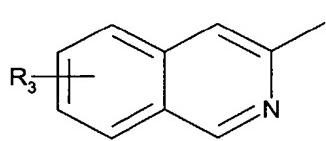
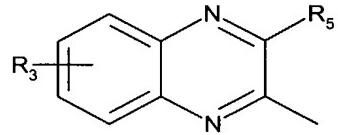
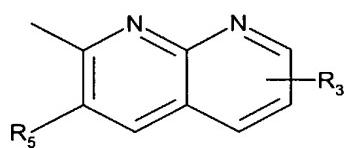
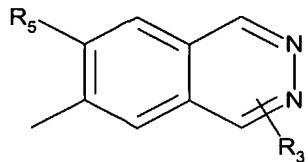
Lp<sub>1</sub> is a cycloalkyl, azacycloalkyl, diazacycloalkyl,  
phenyl, naphthyl, adamantyl, decalinyl, bicycloalkyl, mono-  
or diazabicycloalkyl, mono- or bicyclo heteroaromatic or a  
linear or branched alkyl, alkylene, alkenyl or alkenylene  
15 group all optionally substituted by a group R<sub>3</sub>, or a  
combination of at least two such groups linked by a spiro  
linkage or a single or double bond or by C=O, O, S, SO, SO<sub>2</sub>,  
CONR<sub>1e</sub>-CO-, NR<sub>1e</sub> linkage (for example, representative  
lipophilic groups include a methyl-cyclohexyl,  
20 methylcyclohexylmethyl, bis(piperidinyl, methylphenylmethyl,  
phenylethyl, benzylpiperidinyl, benzoylpiperidinyl or  
phenylpiperazinyl and those as hereinbefore described);

D is a hydrogen bond donor group;

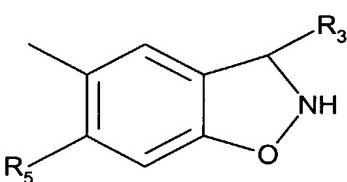
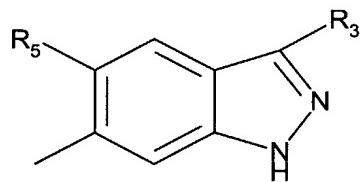
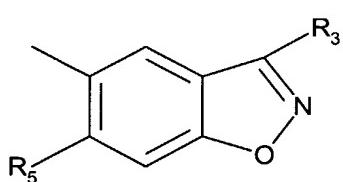
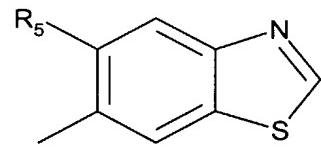
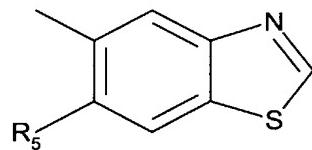
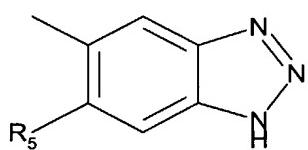
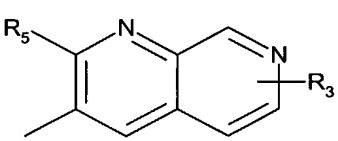
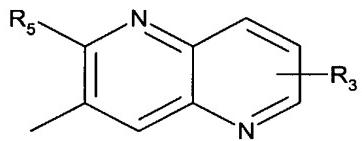
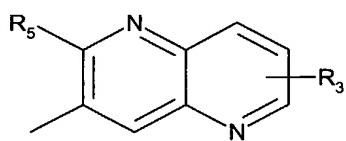
and n is 0, 1 or 2.

25 Suitable R<sub>2</sub> groups may be

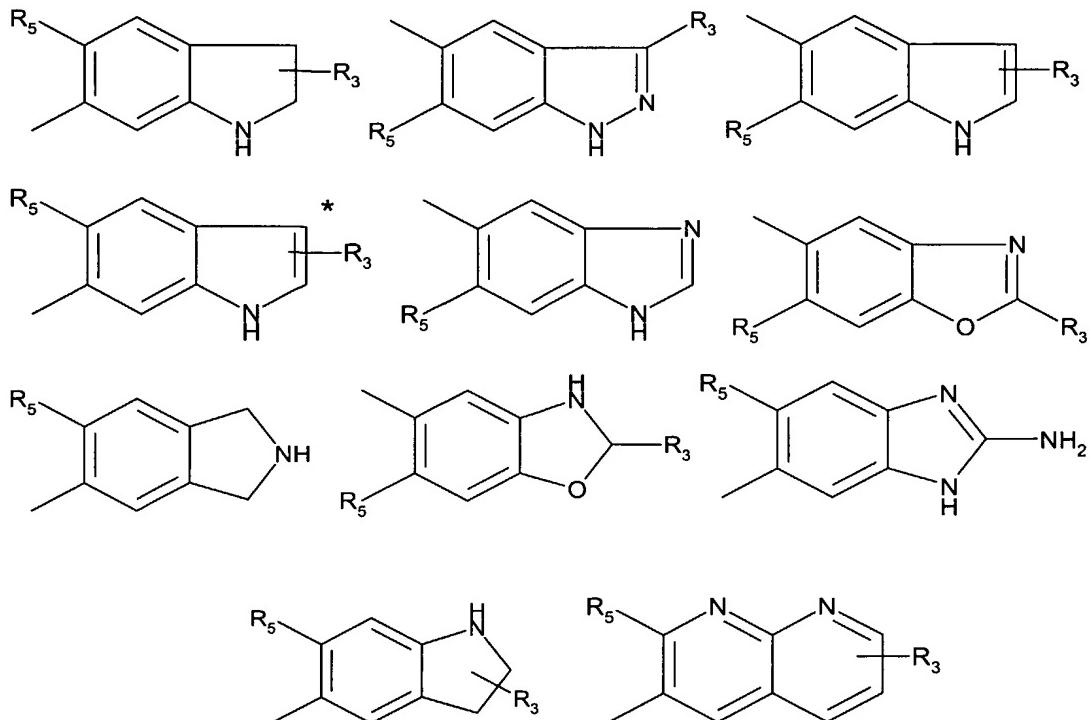




5



10



wherein R<sub>5</sub> is hydrogen, amino or hydroxy and R<sub>3</sub> (in relation to R<sub>2</sub>) is halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>.

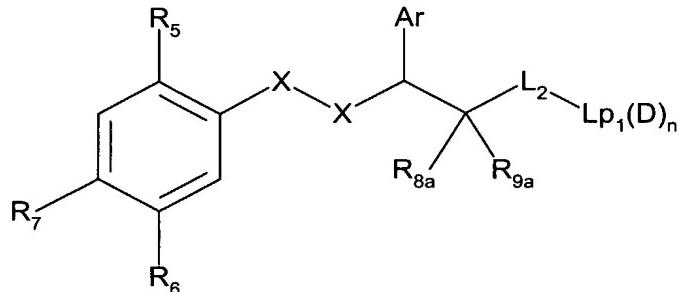
In a particularly favoured embodiment the R<sub>2</sub> group is  
10 an indole as marked by a \* above in which R<sub>5</sub> is hydrogen and R<sub>3</sub> is a hydrogen or halogen present at the 3 position.

It is preferred that at least one of R<sub>6</sub> and R<sub>7</sub> be other than hydrogen and that R<sub>6</sub>, if present, is preferably a substituent containing one or more polar hydrogens such as  
15 hydroxy, amino, alkylamino, aminoalkyl, alkylaminoalkyl, aminocarbonyl, alkylaminocarbonyl, hydrazo and alkylhydrazo; alternatively R<sub>6</sub> and R<sub>7</sub> are joined together in the formation of a naphthyl or indolyl or azaindolyl or diazaindolyl group.

20 It is especially preferred that R<sub>6</sub> be amino and R<sub>7</sub> be chloro, bromo, methyl, methoxy or vinyl; or that R<sub>6</sub> and R<sub>7</sub>

taken together form an indolyl ring with the NH at the 6-position or taken together form a naphthyl ring.

In a further preferred embodiment the compounds of formula (I) are of formula (A)



5

(A)

(wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, Ar, X-X, Lp<sub>1</sub>, D<sub>n</sub> are as hereinbefore defined; L<sub>2</sub> is a valence bond or an organic linker group containing 1 to 3 backbone atoms selected from C, N, O and S and R<sub>8a</sub> and R<sub>9a</sub> are hydrogen or taken together with the carbon atom to which they are attached form a carbonyl group). Again, in an alternative embodiment the phenyl derivative forming part of the R<sub>2</sub> functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

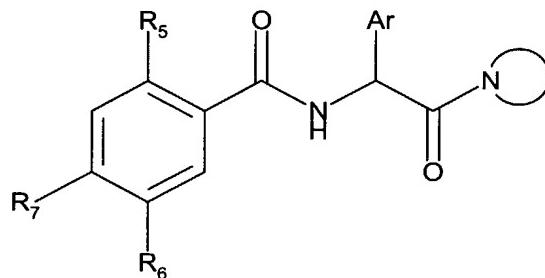
15 In one embodiment, L<sub>2</sub> comprises the backbone of an alpha amino acid, the lipophilic group being the side chain of the amino acid.

In one preferred embodiment R<sub>8a</sub> and R<sub>9a</sub> are hydrogen and L<sub>2</sub> is a OC=O or NHC=O group.

20 In a preferred embodiment, L<sub>2</sub> represents a valence bond and the lipophilic group is bound directly to a carbonyl alpha to the alpha atom via a nitrogen atom which forms part of the lipophilic group. Suitable lipophilic groups in this case therefore include piperidinyl, pyrrolidinyl and  
25 piperazinyl. In a preferred embodiment the piperidine or piperazinyl group is further substituted by a phenyl, benzyl, phenoxy, piperidine, pyridine or benzoyl group,

optionally substituted on the phenyl ring by one or more R<sub>3</sub> groups. In a more preferred embodiment a piperazine is substituted with a phenyl group substituted at the 2-position with an electron withdrawing group such as fluoro, 5 nitro, triazolyl, cyano, alkoxy carbonyl, aminocarbonyl, aminosulphonyl, alkylaminosulphonyl and, especially preferred, alkylsulphonyl; and, at the 4-position, with hydrogen, fluoro, alkoxy or hydroxy. In another more preferred embodiment a piperidine is substituted at the 4- 10 position with 4-piperidine which itself may be substituted on nitrogen by alkyl or aminocarbonylalkyl or alkylaminocarbonyl alkyl.

In a further embodiment, the lipophilic group has attached a group of the formula -COOR<sub>1g</sub> or -CON-aminoacid or 15 ester derivative thereof (where R<sub>1g</sub> is as defined for R<sub>1a</sub>). Particularly preferred compounds are those of formula (G)

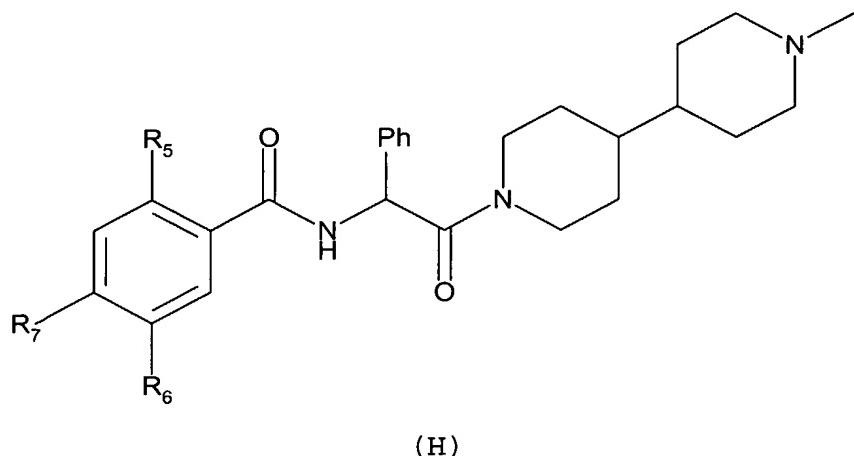


(G)

(wherein Ar, R<sub>6</sub> and R<sub>7</sub> are as hereinbefore defined, R<sub>5</sub> 20 represents hydrogen or amino and



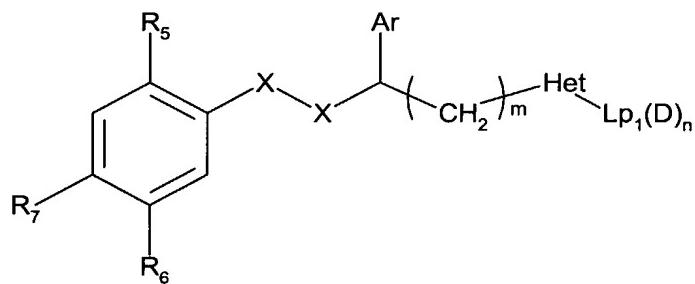
represents a cyclic group) or of formula (H)



(wherein R<sub>6</sub> and R<sub>7</sub> are as hereinbefore defined, and R<sub>5</sub> represents hydrogen or amino). In a preferred embodiment R<sub>6</sub> is 5 amino and R<sub>7</sub> a halogen, especially chlorine.

Again, in an alternative embodiment the phenyl derivative forming part of the R<sub>2</sub> functionality in formulae (G) and (H) may instead be a nitrogen heterocyclic group, e.g. pyridine, indole.

10 In another embodiment the group binding the alpha carbon atom to the lipophilic group comprises a heterocyclic group. Accordingly, preferred compounds of formula (I) also include those of formula (III)



15

(III)

(wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, Ar, X-X, Lp<sub>1</sub>, D<sub>n</sub> are as hereinbefore defined;

m is 0, 1 or 2;

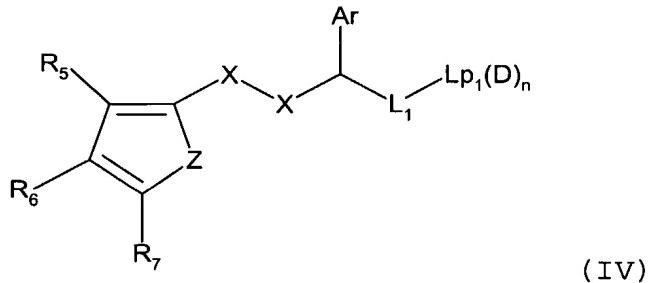
Het is a 5 or 6-membered heterocyclic group interrupted by 1, 2 or 3 heteroatoms selected from O, N and S optionally substituted by a group R<sub>3b</sub> where R<sub>3b</sub> is as defined for R<sub>3</sub>).

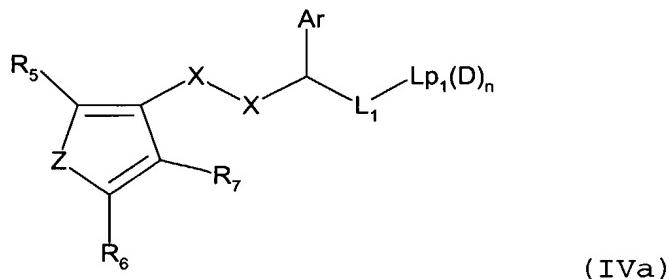
Again, in an alternative embodiment the phenyl derivative forming part of the R<sub>2</sub> functionality may instead be a nitrogen heterocyclic group, e.g. pyridine.

Where Het is a five membered ring, the two ring atoms at which it is connected are preferably separated by one ring atom. Where Het is a six-membered ring, the two ring atoms at which it is connected are preferably separated by one or two ring atoms. Representative heterocyclic groups include thiazole, oxazole, oxadiazole, triazole, thiadiazole or imidazole. Where the heterocyclic group is substituted by R<sub>3b</sub> this is preferably a COOH or COOR<sub>1h</sub> connected to the heterocycle via a valence bond or alkylene chain (where R<sub>1h</sub> is as defined for R<sub>1a</sub>).

In a further embodiment, the lipophilic group has attached a group of the formula -COOR<sub>1g</sub> or -CON-aminoacid or ester derivative thereof.

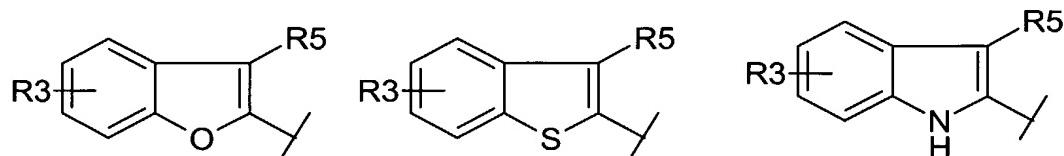
In an alternative embodiment, the main aromatic R<sub>2</sub> ring in the compounds of the invention is a five membered aromatic ring leading to compounds of formula (IV) or (IVa)



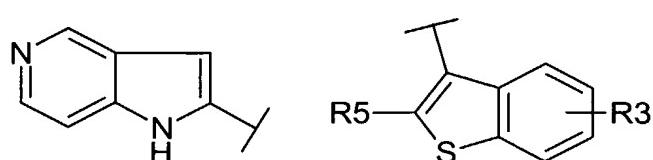
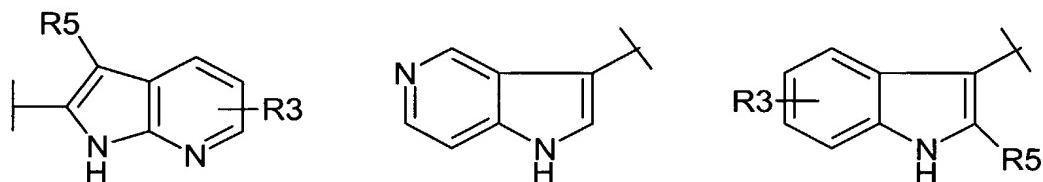


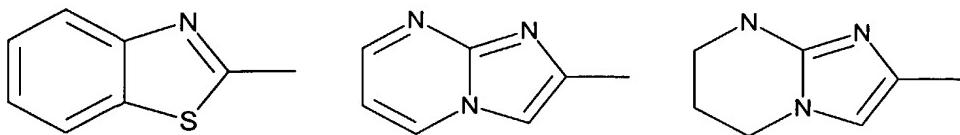
(wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, X-X, Ar, L<sub>1</sub>, Lp<sub>1</sub>, D and n are as hereinbefore described for formula (II) and Z represents N, O or S). It is preferred that at least one of R<sub>6</sub> and R<sub>7</sub> be other than hydrogen, or that R<sub>6</sub> and R<sub>7</sub> taken together enable the formation of an indolyl, or azaindolyl group or diazaindolyl group. Preferences for other substituents are as for formula (A) above. Examples of possible fused systems are given below.

10

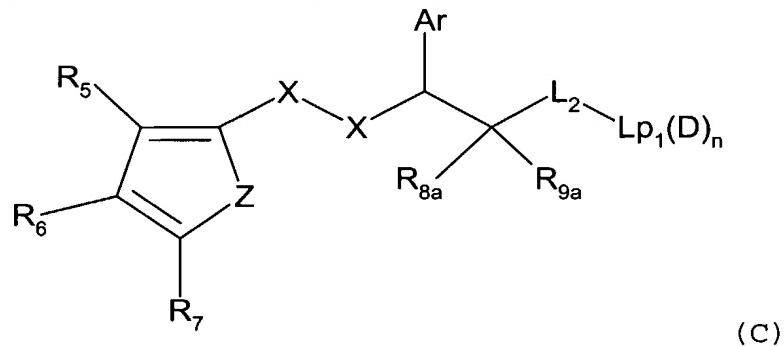


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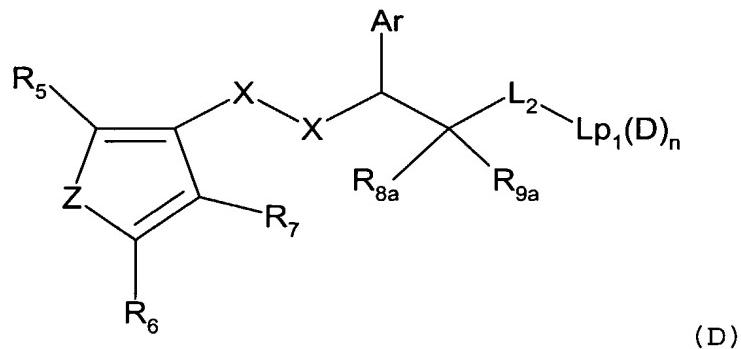




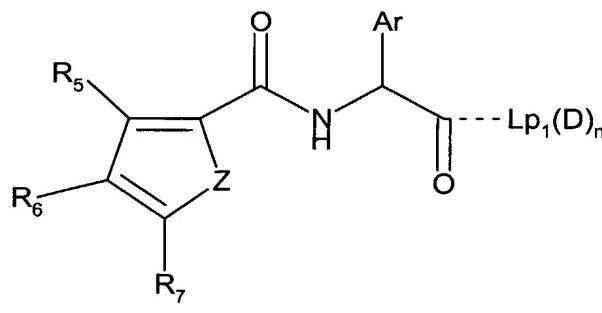
Hence in a preferred embodiment the compounds of the invention are of formula C or D

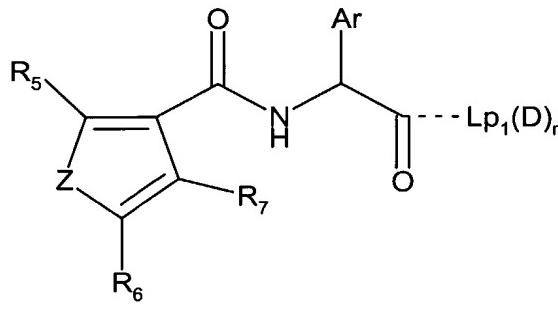


5



(wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, Ar, X-X, Z, R<sub>8</sub>, R<sub>9</sub>, L<sub>2</sub> Lp<sub>1</sub>, D<sub>n</sub> are as hereinbefore defined) preferences for Ar, X-X, R<sub>8a</sub>, R<sub>9a</sub>, L<sub>2</sub>, Lp<sub>1</sub>, D<sub>n</sub> are as for formula (A) above; or compounds of formula E or F:

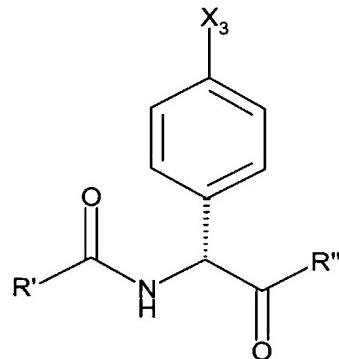




wherein  $Lp_1$  is connected to the carbonyl via a nitrogen atom,  $R_6$ ,  $R_7$ ,  $Ar$ ,  $Z$ ,  $Lp_1$ ,  $D_n$  are as hereinbefore defined and  $R_5$  is hydrogen or amino) preferences for  $Ar$ ,  $Lp_1$ ,  $D_n$  are as 5 for formula (A) above.

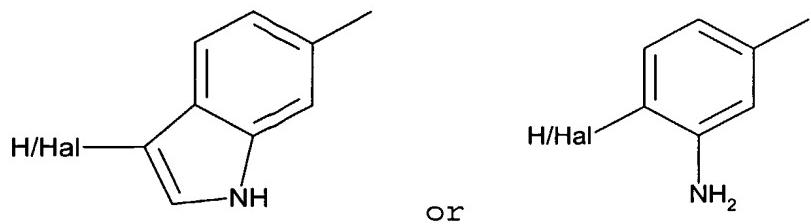
Particularly preferred compounds of formula (I) for use as Factor Xa inhibitors are the compounds of Examples 35, 63, 66, 73, 100, 318 and 320, and physiologically tolerable salts thereof.

10 As previously mentioned, a number of compounds of formula (I) have been found to be excellent mixed inhibitors in that they inhibit both the serine proteases Factor Xa and thrombin. Such mixed inhibitors are preferably based on the formula (L)



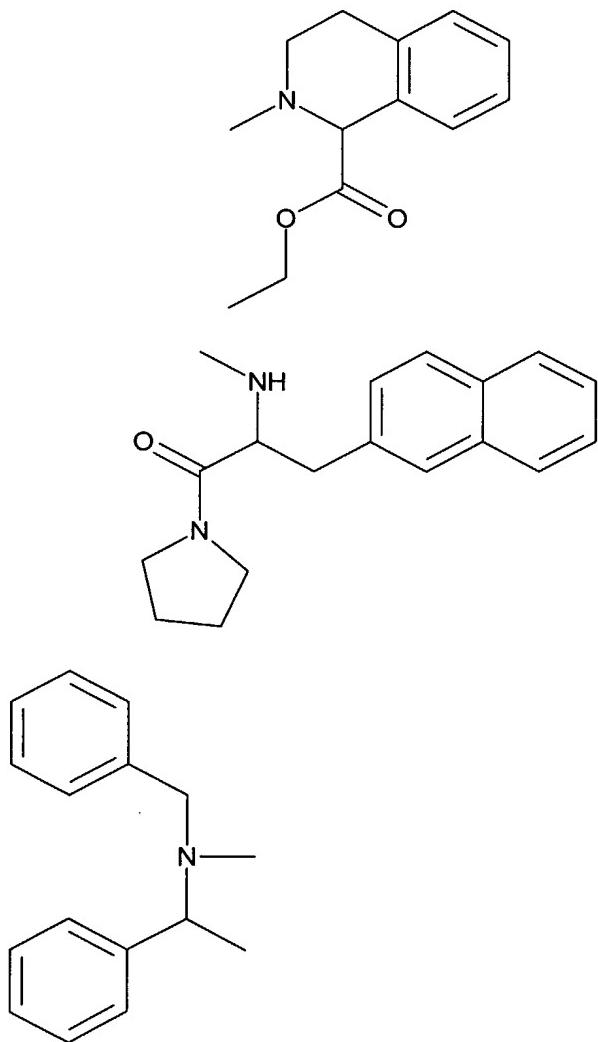
(L)

wherein  $R'$  represents

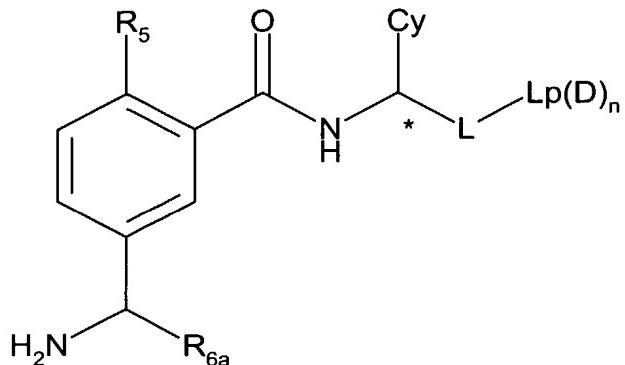


X<sub>3</sub> represents hydrogen or a polar group such as amino or CONH<sub>2</sub>, especially CONH<sub>2</sub>; and

- 5 R" represents a cyclic group bound to the carbonyl by a nitrogen atom or an optionally substituted group of formula



tryptase inhibitors is that of formula



in which:

L-Lp(D)<sub>n</sub> represents CO-L<sub>x</sub>;

- 5      R<sub>5</sub> represents amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen;
- 10     R<sub>6a</sub> represents hydrogen or methyl;
- Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, preferably containing 5 to 10 ring atoms and optionally substituted by groups R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub>;
- 15     each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, hydrazido, alkylsulphonamido, alkylamino-sulphonyl, aminosulphonyl, haloalkoxy, and haloalkyl;

each  $R_{1c}$  independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxylalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, 5 aryl or cycloalkyl;

$L_x$  is a mono or bicyclic group bound to the carbonyl via a pendent nitrogen atom or nitrogen atom which forms part of the mono or bicyclic ring;

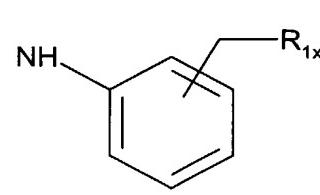
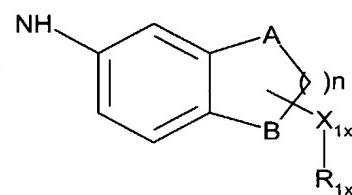
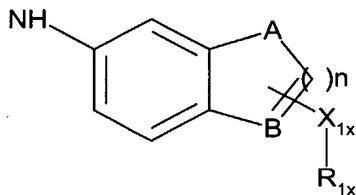
or a physiologically tolerable salt thereof, e.g. a 10 halide, phosphate or sulphate salt or a salt with ammonium or an organic amine such as ethylamine or meglumine.

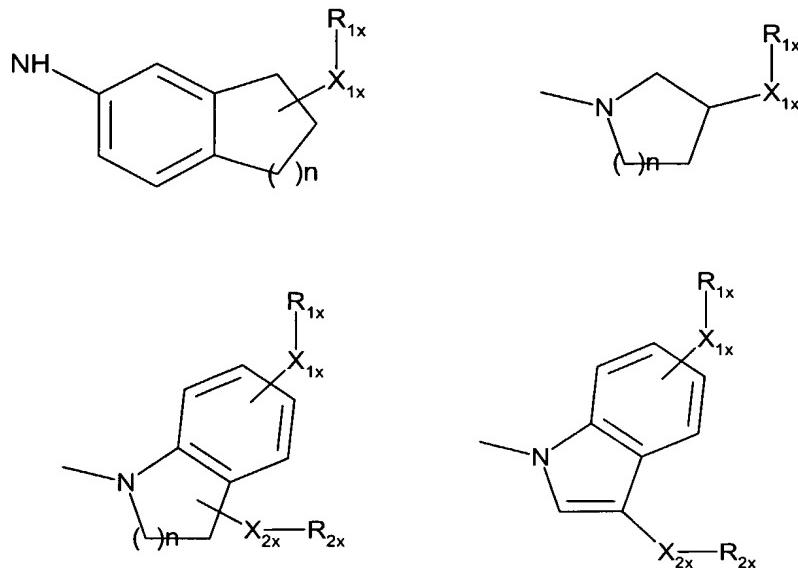
It will be appreciated that when  $L_x$  is bound to the carbonyl via a pendant nitrogen, the group  $CO-L_x$  corresponds with the group  $L-Lp(D)_n$  in which L is CONH and Lp is a mono 15 or bicyclic group. When  $L_x$  is bound to the carbonyl via a nitrogen that forms part of the mono or bicyclic ring, the group  $CO-L_x$  corresponds with the group  $L-Lp(D)_n$  in which L is CO and Lp is a mono or bicyclic group containing a nitrogen atom in the ring and bound to L via this nitrogen.

20 It is believed that an aminomethyl group positioned on the 3 position of the phenyl ring will give rise to excellent binding within the S1 binding pocket of tryptase. Without wishing to be limited by theory it is believed that the presence of a hydrogen bond donating group attached to 25 the phenyl group will be essential for successful inhibition of tryptase.

$R_5$  and  $R_6$  are both preferably hydrogen.

Most preferably the  $L_x$  group comprises





5 wherein:

A and B are independently chosen from NH, N, O, S, CH,  
CH<sub>2</sub>;

X<sub>1x</sub> and X<sub>2x</sub> are independently chosen from  
(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m</sub>CH=CH(CH<sub>2</sub>)<sub>p</sub>, CO(CH<sub>2</sub>)<sub>m</sub>, NH(CH<sub>2</sub>)<sub>m</sub>, NHCO(CH<sub>2</sub>)<sub>m</sub>,  
CONH(CH<sub>2</sub>)<sub>m</sub>, SO<sub>2</sub>NH(CH<sub>2</sub>)<sub>m</sub>, NHSO<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>;

n is 1 or 2;

m is 0 to 2;

p is 0 to 2;

R<sub>1x</sub> and R<sub>2x</sub> are independently chosen from hydrogen,  
15 alkoxy, alkyl, aminoalkyl, hydroxyalkyl, alkoxyalkyl,  
alkoxycarbonyl, amino, halo, cyano, nitro, thiol, alkylthio,  
alkylsulphonyl, alkylsulphenyl, oxo, heterocyclo optionally  
substituted by R<sub>3x</sub>, cycloalkyl optionally substituted by R<sub>3x</sub>  
or aryl optionally substituted by R<sub>3x</sub>; and

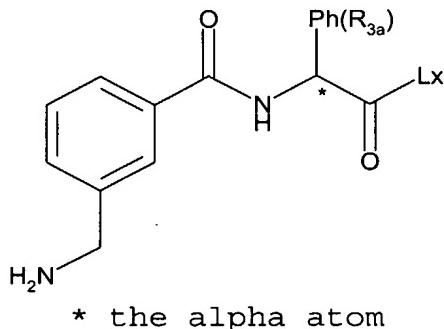
20 R<sub>3x</sub> is hydrogen, alkoxy, alkyl, amino, hydroxy, alkoxy,  
alkoxycarbonyl, halo, cyano, nitro, thiol, sulphonyl, or  
sulphenyl.

Examples of heterocyclic R<sub>1x</sub> and R<sub>2x</sub> groups are  
piperidine, piperazine and pyrrolidine.

The cyclic group attached to the alpha atom is preferably an optionally  $R_{3a}$  substituted phenyl.

Thus, one group compounds of formula (I) of interest as tryptase inhibitors are those of formula (II)

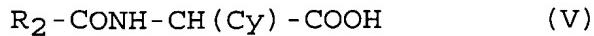
5



II

wherein  $Lx$  is as hereinbefore defined. It is envisaged that  
10 especially preferred  $Lx$  groups will be those in which a cyclic or bicyclic ring is substituted by hydrogen bond donating and/or acceptor groups.

The compounds of formula (I) may be prepared by conventional chemical synthetic routes or by routes as  
15 illustrated by the following examples, e.g. by amide bond formation to couple the aromatic function to the alpha atom and to couple the lipophilic function to the alpha atom. Where the alpha atom is a carbon, the cyclic group-alpha atom combination may conveniently derive from an alpha amino acid with the aromatic deriving from for example an acid derivative of a compound based on  $R_2$ , e.g. o-amino-benzoic acid or aminomethylbenzoic acid. Amide formation from such reagents (in which any amino or hydroxyl function especially in an aminomethyl group) may if desired be  
20 protected during some or all of the synthesis steps) yields a compound of formula (V).

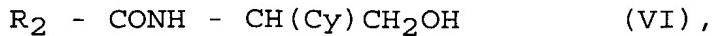


(where Cy and R<sub>2</sub> are as defined above).

Prior to reaction the amino group in an aminoalkyl  
5 group should be protected by an appropriate protecting group  
e.g. Boc, Z, Fmoc or Bpoc. The use of protecting groups is  
described in McOmie, "Protective Groups in Organic  
Chemistry", Plenum, 1973 and Greene, "Protective Groups in  
Organic Synthesis", Wiley Interscience, 1981.

10 The lipophilic group (and optionally simultaneously the  
hydrogen bond donor) may then conveniently be introduced by  
reaction of a compound of formula (V) (or another analogous  
carboxylic acid) optionally after transformation into an  
activated form, e.g. an acid chloride or active ester, with  
15 a lipophilic group carrying an amine, hydroxylamine,  
hydrazine or hydroxyl group, e.g. to produce compounds with  
linkages of -CO-NR<sub>1d</sub>- , -CO-NR<sub>1d</sub>-O- , -CO-NR<sub>1d</sub>-NR<sub>1d</sub>- and  
-CO-O- from the alpha atom (where it is a carbon) to the  
lipophilic group. Cyclisation can be base induced via  
20 nucleophilic attack of the alpha atom on a leaving group on  
the active side chain. If necessary the amide linkage can  
be reduced using an appropriate reducing agent employing the  
necessary protection depending on whether concurrent  
reduction of the carboxylic acid moiety is also desired.  
25 Alternatively a compound of formula V or another analogous  
carboxylic acid may be transformed into an alcohol by  
reaction with isobutylchloroformate and reduction with  
sodium borohydride.

Such an alcohol, e.g. of formula VI



can be reacted to introduce the lipophilic group by reactions such as:

alkylation with an alkyl halide in the presence of a base;

5 under Mitsunobu conditions, such as reaction with diethyl azodicarboxylate/triphenylphosphine and a hydroxylated aryl compound;

10 by reaction with an activated carboxylic acid (e.g. an acid chloride) or with a carboxylic acid and diethylazodicarboxylate/triphenylphosphine;

by reaction with an isocyanate; and

15 by treatment with methanesulphonyl chloride or trifluoromethanesulphonic anhydride and reaction with an amine, or with a thiol optionally followed by oxidation, e.g. with potassium metaperiodate or hydrogen peroxide.

Alternatively, the reactions described above may be performed on a corresponding compound of formula (VI) in which R<sub>2</sub> is replaced with a protecting group, such as t-butoxycarbonyl (Boc), followed by deprotection and introduction of the group R<sub>2</sub>.

In this way compounds with linkages of -CH<sub>2</sub>-O-, -CH<sub>2</sub>-O-CO-, -CH<sub>2</sub>-O-CO-NR<sub>1d</sub>-, -CH<sub>2</sub>-NR<sub>1d</sub>-, -CH<sub>2</sub>-S-, -CH<sub>2</sub>-SO- and -CH<sub>2</sub>-SO<sub>2</sub>- between the alpha carbon and the lipophilic group may be produced.

25 Alternatively the alcohol can be oxidized to form a corresponding aldehyde (e.g. by oxidation with manganese dioxide or DMSO/oxalyl chloride or DMSO/SO<sub>3</sub> or Dess-Martin reagent) which may be reacted to introduce the lipophilic group by reactions such as:

30 reaction with Wittig reagents or Horner-Emmons reagents, optionally followed by reduction of the resulting carbon:carbon double bond using H<sub>2</sub>/Pd-carbon;

reaction with an organometallic, eg a Grignard reagent, optionally followed by reaction on the resulting hydroxyl group, such as oxidation (eg with  $MnO_2$ , DMSO/oxalyl chloride or Dess-Martin reagent), alkylation (eg with an alkyl halide in the presence of a base in a solvent such as DMF), arylation (eg with diethylazo dicarboxylate/triphenyl phosphine and a hydroxyaryl compound), ester formation (eg with an acid chloride or with a carboxylic acid and diethylazido dicarboxylate/triphenyl phosphine), or carbamate formation (eg with an isocyanate);  
5 by reaction with an amine followed by reduction, e.g. with sodium cyanoborohydride;  
by reaction with a hydrazine; or  
10 by reaction with a carbazide.  
15 In this way compounds with linkages of  $-CH=CR_{1d}-$ ,  $-CH_2-CHR_{1d}-$ ,  $-CHOH-$ ,  $-CHR_{1d}-O-$ ,  $-CHR_{1d}-O-CO-$ ,  $-CHR_{1d}-O-CO-NR_{1d}-$ ,  $-CO-$ ,  $-CH_2-NR_{1d}-$ ,  $-CH=N-NR_{1d}-$  and  $-CH=N-NR_{1d}-CO-NR_{1d}-$  between the alpha carbon and the lipophilic group may be produced.

20 The transformation of alcohol to amine referred to above may be used to produce an amine reagent for lipophilic group introduction, e.g. a compound

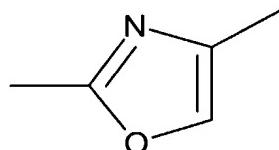


Such an amine reagent may be reacted to introduce the 25 lipophilic group, e.g. by acylation with an acid halide or activated ester, by reaction with isocyanate, by reaction with an isothiocyanate, or by reaction with a sulphonyl chloride. In this way compounds with linkages of  $-CH_2NR_{1d}-CO-$ ,  $-CH_2-NR_{1d}-CO-NR_1-$ ,  $-CH_2NR_{1d}-CS-NR_{1d}-$  and  $-CH_2NR_{1d}-SO_2-$  30 between the alpha carbon and the lipophilic groups may be produced.

The transformation of acid to amide referred to above may be used to produce an amide reagent for introduction of the lipophilic group, e.g. a compound

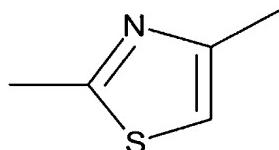


Such amides may be reacted to introduce lipophilic groups, e.g. by reaction with a haloketone (e.g. phenacyl bromide). This provides a linkage

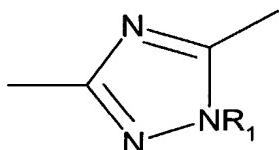


from alpha carbon to lipophilic group.

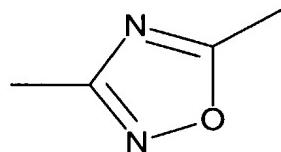
Analogously the amide may be transformed to a thioamide by reaction with Lawesson's reagent and then reacted with a haloketone to form a linkage



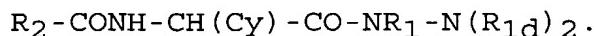
The amide reagent may likewise be transformed to a nitrile reagent by dehydration, e.g. with trifluoroacetic anhydride. The nitrile reagent may be reacted with hydrazine then with acyl halide and then cyclized, (e.g. with trifluoroacetic anhydride) to produce a linkage



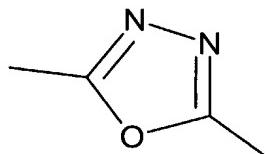
Alternatively it may be treated with hydroxylamine then reacted with acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce a linkage



The hydrazide produced by reaction of a carboxylic acid reagent with hydrazine discussed above may likewise be used as a reagent for lipophilic group introduction, e.g. as a  
5 compound of formula



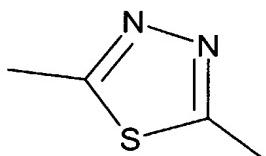
Thus the hydrazide reagent can be reacted with an acyl halide and cyclized, e.g. with trifluoroacetic anhydride to yield a linkage



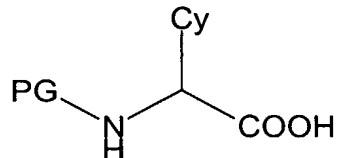
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or reacted with an acyl halide or an isocyanate to yield linkages  $\text{-CO-NR}_{1d}\text{-NR}_{1d}\text{-CO-}$  and  $\text{-CO-NR}_{1d}\text{-NR}_{1d}\text{-CO-NR}_{1d}\text{-}$  respectively.

Alternatively the hydrazide may be transformed by  
15 reaction with Lawesson's reagent and then reacted with an acyl halide and cyclized (e.g. with trifluoroacetic anhydride) to produce the linkage



An alternative route to these compounds is to carry out  
20 any of the above chemical reactions to incorporate the lipophilic group (and optional H bond donor) into a protected intermediate such as a compound of formula (VII).



PG = Protecting group

The protecting group may then be removed before coupling of the for example o-amino benzoic acid (optionally 5 protected).

The protection of amino and carboxylic acid groups is described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, 10 NY, 1991. Examples of carboxy protecting groups include C<sub>1</sub>-C<sub>6</sub> alkyl groups such as methyl, ethyl, t-butyl and t-amyl; aryl(C<sub>1</sub>-C<sub>4</sub>)alkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl 15 and trityl; silyl groups such as trimethylsilyl and t-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl.

Examples of amine protecting groups (PG) include acyl groups, such as groups of formula RCO in which R represents 20 C<sub>1-6</sub> alkyl, C<sub>3-10</sub> cycloalkyl, phenyl C<sub>1-6</sub> alkyl, phenyl, C<sub>1-6</sub> alkoxy, phenyl C<sub>1-6</sub> alkoxy, or a C<sub>3-10</sub> cycloalkoxy, wherein a phenyl group may be optionally substituted, for example by one or two of halogen, C<sub>1-C<sub>4</sub></sub> alkyl and C<sub>1-C<sub>4</sub></sub> alkoxy.

Preferred amino protecting groups include benzyloxycarbonyl (CBz), t-butoxycarbonyl (Boc) and benzyl.

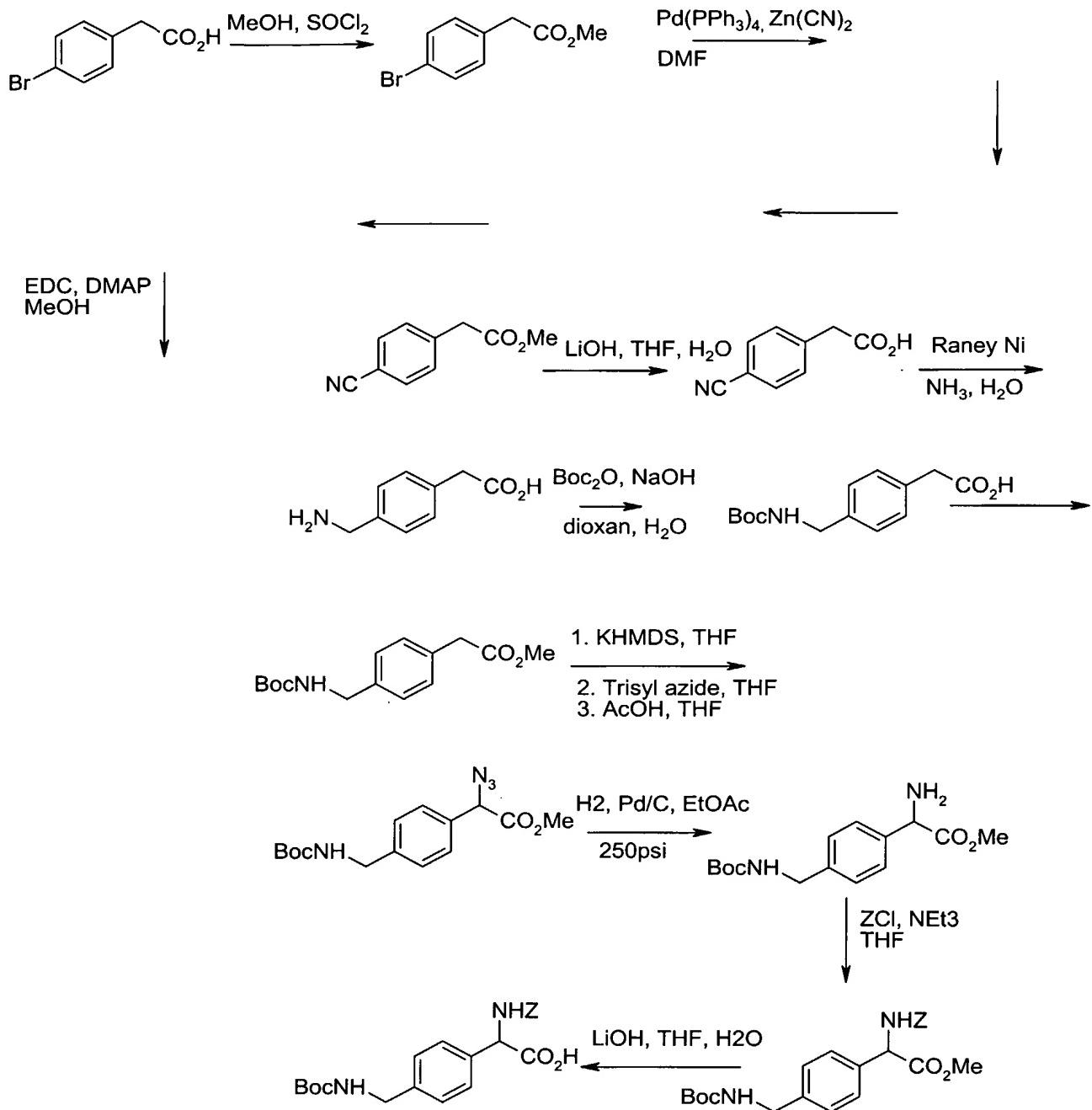
$\alpha$ -Amino acids of formula (VII) which are not commercially available can be synthesized by methods known in the art, for example as described in "Synthesis of Optically Active  $\alpha$ -Amino Acids" by Robert M. Williams

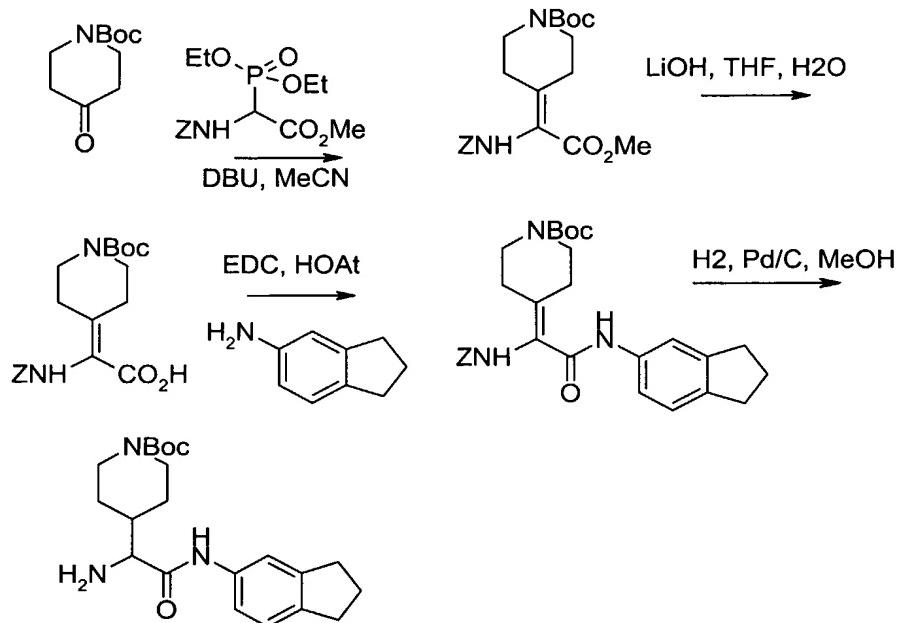
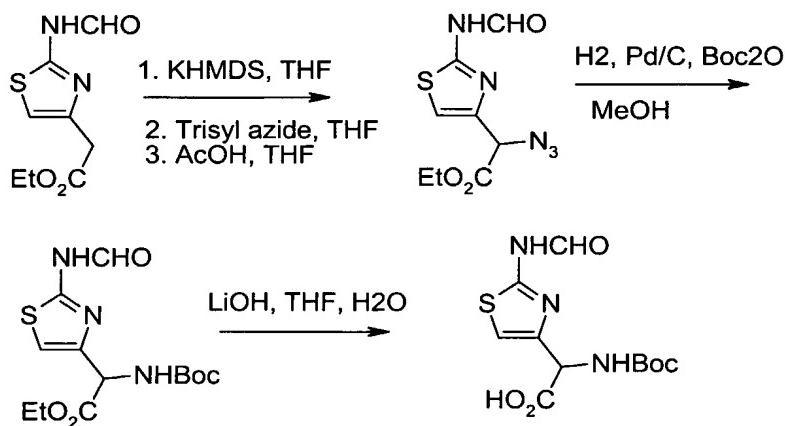
(Pergamon Press, 1989) and "Asymmetric Synthesis of ArylGlycines", Chem. Rev. 1992, 889-917.

Compounds of the type (VII) made be prepared (for example) by one or more of the following methods.

- 5     (i) from aryl or heteroaryl aldehydes via the Strecker synthesis or modifications thereof, via Bucherer-Bergs hydantoin synthesis, or via the Ugi methodology (Isonitrile Chemistry, Ugi I. Ed.; Academic: New York, 1971; pp145-199) with removal and replacement of protecting groups;
- 10    (ii) from styrenes via Sharpless methodology (J. Am. Chem. Soc. 1998, 120, 1207-1217)
- (iii) from aryl boronic acids via Petasis methodology (Tetrahedron, 1997, 53, 16463-16470) with removal and replacement of protecting groups;
- 15    (iv) from aryl and heteroaryl acetic acids - via Evan's azidation (Synthesis, 1997, 536-540) or by oximation, followed by reduction and addition of protecting groups; or
- (v) from existing aryl glycines by manipulation of functional groups, for example, alkylation of hydroxy groups, palladium assisted carbonylation of triflates derived from hydroxy groups and further manipulation of the carboxylic esters to give carboxylic acids by hydrolysis, carboxamides by activation of the carboxylic acid and coupling with amines, amines via Curtius reaction on the carboxylic acid or
- 20    (vi) from aliphatic, carbocyclic and non-aromatic heterocyclic aldehydes and ketones using a Horner-Emmons reaction with N-benzyloxycarbonyl)- $\alpha$ -phosphonoglycine trimethyl ester (Synthesis, 1992, 487-490).

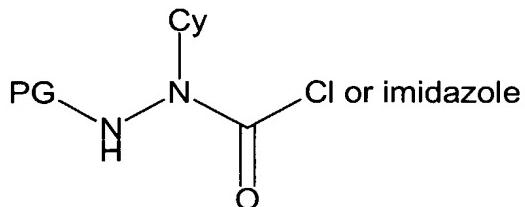
30           Examples of synthetic routes are shown below:



**Synthesis of protected 4-piperidylglycine****Synthesis of protected 2-aminothiaz-4-ylglycine**

A starting reagent for lipophilic group introduction where the alpha atom is nitrogen may be produced for example by reaction of a beta protected hydrazine (such protection 5 to be chosen as to be compatible with the subsequent reagents to be employed) with phosgene, diphosgene,

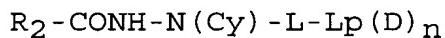
triphosgene or N,N'carbonyl diimidazole to give a reactive compound of the type:



PG = Protecting group

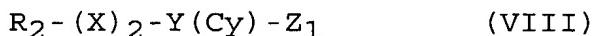
5 This intermediate may be used as has been described above for the carboxylic starting reagents where the alpha atom is carbon.

Removal of the protecting group by standard methods and coupling with an activated aryl carboxylic acid will give  
10 compounds of the type



(where R<sub>2</sub>, X, Y, Cy, L, Lp and D are as defined above).

15 Thus the compounds of formula (I) may be prepared by a process which comprises coupling a lipophilic group to a compound of formula (VIII)



20

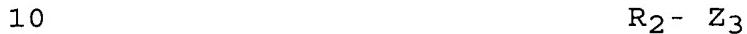
(wherein R<sub>2</sub>, X, Y and Cy are as defined above and Z<sub>1</sub> is a reactive functional group), and optionally subsequently coupling a hydrogen bond donor group to said lipophilic group.

25 Instead of introducing the group L-Lp(D)<sub>n</sub> as the final stage process step, the compounds of formula I may alternatively be prepared by a process in which the group R<sub>2</sub> is introduced in the final process step.

Thus the compounds of formula (I) may also be prepared by a process which comprises coupling a lipophilic group to a compound of formula (IX)



(wherein Y, Cy, L, Lp D, and n are as defined above and  $Z_2$  is HX or a reactive functional group), or a protected derivative thereof, with a compound of formula (X)



(wherein  $R_2$  is as defined above and  $Z_3$  is XH or an appropriate reactive group), or a protected derivative thereof, followed if necessary by the removal of any protecting groups.

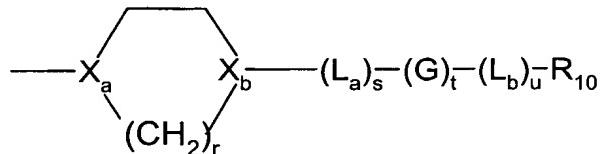
15                  Thus, for a compound of formula I in which X-X represents CONH, a compound of formula (IX) in which  $Z_2$  is  $H_2N$  may be reacted with a compounds of formula (X) in which  $Z_3$  is COOH or a reactive derivative thereof, such as a acyl halide or an anhydride, for example as described in the

20 Examples herein.

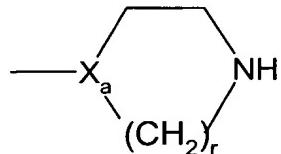
Where the lipophilic group Lp comprises more than one group, it may generally be formed by coupling these groups together at an appropriate stage in the preparation of the compound of formula I using conventional methods or as

25 described in the Examples.

For a compound of formula I in which Lp comprises an azacycloalkyl or diazacycloalkyl group of formula

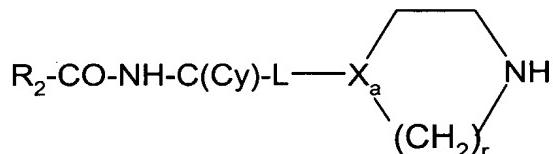


in which  $X_b$  is N and each of s and u is 0, alkylating the amino group of a corresponding compound in which the corresponding residue is of formula



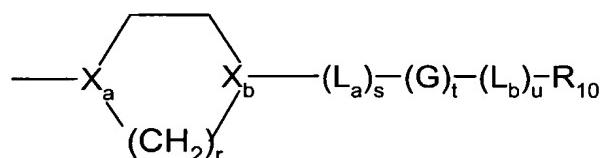
5 using a conventional alkylating method. The alkylation may be carried out using any conventional method; however, generally preferred is a reductive alkylation using the appropriate aldehyde or ketone, for example as described in the Alkylation Methods in the Examples.

10 Thus, a particular starting material for the alkylation is one of formula

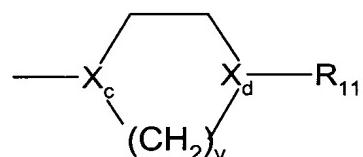


in which  $X_a$  is N and L is CO or  $X_a$  is CH and L is CONH, CONHCH<sub>2</sub> or CH<sub>2</sub>NHCO.

15 For a compound of formula I in which L<sub>p</sub> comprises an azacycloalkyl or diazacycloalkyl group of formula



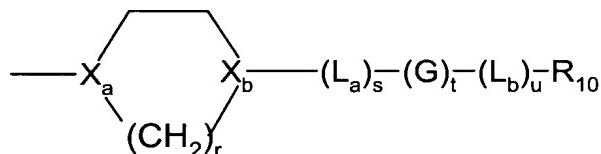
20 in which R<sub>10</sub> is a group of formula



in which  $X_d$  is N and  $R_{11}$  is (1-6C)alkyl, alkylating the amino group of a corresponding compound of formula I in which  $R_{11}$  is hydrogen using a conventional method.

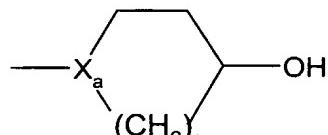
Generally preferred is a reductive alkylation using the  
5 appropriate aldehyde or ketone, for example as described in the Alkylation Methods in the Examples.

For a compound of formula I in which  $L_p$  comprises an azacycloalkyl or diazacycloalkyl group of formula



10

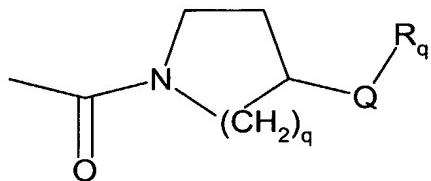
in which  $X_b$  is CH and  $(L_a)_s - (G)_t - (L_b)_u$  is O and  $R_{10}$  is phenyl or pyridyl, coupling a corresponding compound containing a group of formula



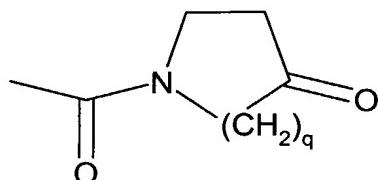
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with phenols or 3-hydroxypyridine using Mitsunobu conditions, e.g. DEAD (diethyl azodicarboxylate) /Ph<sub>3</sub>P or 2-triphenylphosphonium 4,4-dimethyl-tetrahydro-1,2,5-thiadiazole to give aryloxy or 3-pyridoxy substituted piperidines or pyrrolidine. Alternatively the hydroxy group may be reacted with sodium hydride and 2-chloro or 4-chloropyridine to give 2-pyridoxy or 4-pyridoxy substituted piperidines or pyrrolidines.  
20

For a compound of formula I in which -L-Lp(D)<sub>n</sub> is

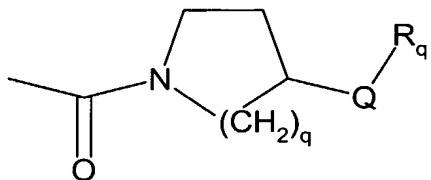


in which Q is a direct bond, reductively alkylating an amine of formula H-Q using a corresponding compound in which the corresponding residue is a ketone of formula

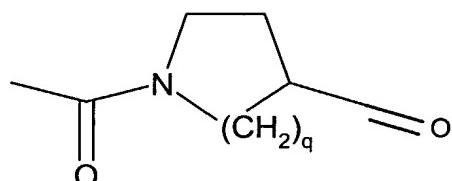


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For a compound of formula I in which  $-L-Lp(D)_n$  is



in which Q is methylene, reductively alkylating an amine of formula H-NR<sub>a</sub>R<sub>b</sub> using a corresponding compound in which the 10 corresponding residue is an aldehyde of formula



For example, methyl 1-acetyl-3-formylindole-6-carboxylic acid may be converted to the 3-formate by the method of Merour et al (Synthesis, 1994, 411) and then 15 reacted with trimethyl orthoformate to give methyl 1-acetyl-3-methoxyindole-6-carboxylate which is then hydrolysed to methyl 1-acetyl-3-methoxyindole-6-carboxylate.

5-Fluoroindole-6-carboxylic acid may be prepared from 4-fluoro-3-methoxyaniline by the following method. 4-Fluoro-

3-methoxyaniline is treated with glyoxal-1,1-dimethyl acetal and then hydrogenated over Pd/C. The product is N-protected with methanesulphonyl chloride and then cyclised using titanium tetrachloride in toluene. Demethylation with BBr<sub>3</sub>

5 to the phenol followed by reaction with triflic anhydride and then palladium carbonylation in methanol gives the methyl ester, which is then converted to 5-fluoro-1-methanesulphonylindole-6-carboxylic acid by hydrolysis with lithium hydroxide. This 'benzoyl' component may be reacted

10 as previously described and deprotected by hydrolysis with sodium hydroxide at 100°C.

The compounds of formula (I) may be administered by any convenient route, e.g. into the gastrointestinal tract (e.g. rectally or orally), the nose, lungs, musculature or

15 vasculature or transdermally. The compounds may be administered in any convenient administrative form, e.g. tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches etc. Such compositions may contain components

20 conventional in pharmaceutical preparations, e.g. diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents. Preferably the compositions will be sterile and in a solution or suspension form suitable for injection or infusion. Such compositions form a further

25 aspect of the invention.

The following are examples of pharmaceutical compositions of compounds of formula (I) or physiologically tolerable salts thereof.

**Formulation 1**

Hard gelatin capsules are prepared using the following ingredients:

5

		Quantity (mg/capsule)
10	Active Ingredient	250
	Starch, dried	200
	Magnesium stearate	<u>10</u>
15	Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

20

**Formulation 2**

Tablets each containing 60 mg of active ingredient are made  
as follows:

5

	Active Ingredient	60 mg
	Starch	45 mg
	Microcrystalline cellulose	35 mg
10	Polyvinylpyrrolidone	4 mg
	Sodium carboxymethyl starch	4.5 mg
	Magnesium stearate	0.5 mg
	Talc	<u>1 mg</u>
15	Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The 20 solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, 25 previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

It is believed that the compounds of the invention will have excellent oral bioavailability.

30 Thus the compounds of formula (I) and their physiologically tolerable salts will generally be administered to a patient in pharmaceutical composition which

comprises a serine protease inhibitor of formula (I) together with at least one pharmaceutically acceptable carrier or excipient. The pharmaceutical composition may also optionally comprise at least one further antithrombotic 5 and/or thrombolytic agent.

The dosage of the inhibitor compound of formula (I) will depend upon the nature and severity of the condition being treated, the administration route and the size and species of the patient. However in general, quantities of 10 from 0.01 to 100  $\mu\text{mol}/\text{kg}$  bodyweight will be administered.

All publications referred to herein are hereby incorporated by reference.

The following non-limiting Examples illustrate the preparation of compounds of formula (I) for use as serine 15 protease inhibitors according to the invention.

Examples - Part 1Experimental

Abbreviations used follow IUPAC-IUB nomenclature.

- 5 Additional abbreviations are Hplc, high-performance liquid chromatography; DMF, dimethylformamide; DCM, dichloromethane; HAOT, 1-hydroxy-7-azabenzotriazole; HATU, [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate]; Fmoc, 9-Fluorenylmethoxycarbonyl;
- 10 HOEt, 1-hydroxybenzotriazole; TBTU, 2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate; EDCI, 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DIPEA, diisopropylethylamine; Boc, tertiary butyloxycarbonyl; DIPCI, diisopropylcarbodiimide; DBU, 1,8-15 diazabicyclo[5.4.0]undec-7-ene; TEA, triethylamine; Rink linker, p-[(R,S)- $\alpha$ -[1-(9H-Fluoren-9-yl)methoxyformamido]-2,4-dimethoxybenzyl]phenyl acetic acid; TFA, trifluoroacetic acid; MALDI-TOF, Matrix assisted laser desorption ionisation - time of flight mass spectrometry, RT, retention time.
- 20 Amino acid derivatives, resins and coupling reagents were obtained, for example, from Novabiochem (Nottingham, UK) and other solvents and reagents from Rathburn (Walkerburn, UK) or Aldrich (Gillingham, UK) and were used without further purification. All solution concentrations are expressed as
- 25 %Vol./%Vol. unless otherwise stated.

**Purification:** Purification was by gradient reverse phase Hplc on a Waters Deltaprep 4000 at a flow rate of 50 ml/min. using a Deltapak C18 radial compression column (40 mm x 30 210 mm, 10-15 mm particle size). Eluant A consisted of aqTFA (0.1%) and eluant B 90% MeCN in aq TFA(0.1%) with gradient elution (Gradient 1, 0 min. 20%B then 20% to 100%

over 36 min., Gradient 2, 0 min. 5% B for 1 min. then 5% B to 20% B over 4 min., then 20% to 60% over 32 min. or Gradient 3, 0 min. 20% B then 20% to 100% over 15 min.). Fractions were analysed by analytical Hplc and MALDI-TOF before 5 pooling those with >95% purity for lyophilisation.

**Analysis:** Analytical Hplc was on a Shimadzu LC6 gradient system equipped with an autosampler, a variable wavelength detector at flow rates of 0.4 ml/ min. Eluents A and B as 10 for preparative Hplc. Columns used were Techogell5 C18 (2x150mm) (Hplc Technology), Magellan C8 column (2.1x150 mm, 5 $\mu$ m particle size) and Luna C18 (2.1x150 mm, 5 $\mu$ M particle size). (Phenomenex)) Purified products were further analysed by MALDI-TOF and nmr. NMR denotes an  $^1$ HNMR consistent with 15 the structure was obtained.

#### Synthesis of inhibitors

**Method 1:** Using a solid phase strategy on a Protein 20 Technologies, Symphony Multiple Peptide Synthesiser by attachment of bis amino compounds to Peg-trityl chloride resin: Trityl chloride resin was typically treated with greater than 2 fold excess of the di-amino in dry DCM .The resin was further modified by the attachment of acids. 25 Activation of Fmoc protected amino acid (2-5eq) was by TBTU/DIPEA, all couplings ( minimum 120 min.) were carried out in DMF. Deprotection of the Fmoc group was achieved with 20% piperidine in DMF. In the next stage other acid substituents were added as the HOBt or HOAt esters either by activation 30 with HBTU/HATU or HATU/EDCI with or without Boc protection of amino groups. Cleavage of the products from the resin was by treatment (30 min., ambient) with 10% triethylsilane in

TFA, filtration, evaporation and trituration with diethylether.

Synthesis using the Symphony Multiple Peptide Synthesiser.

5

The Symphony Multiple Peptide Synthesiser is charged with DMF, DCM, TBTU in DMF(450 mM), DIPEA in DMF (900 mM), 20% piperidine in DMF. Resins are held in plastic reaction vessels that allow the introduction of reagents and solvents 10 and nitrogen for agitation or air drying.

A typical synthesis cycle on the Symphony is as follows:-

The reaction vessel containing the resin (0.1 mmol) is 15 charged with the Fmoc protected amino acid (0.5 mmol) and then this is dissolved in DMF (2.5ml), treated with TBTU (0.56 mmol, 1.25ml) and DIPEA (1.1 mmol, 1.25ml) and agitated with nitrogen for 2 hours (agitation times may vary). After coupling the resin is washed with DMF (6x 5ml) 20 then deprotected with 20% piperidine in DMF (2x 5ml for 1 min.each, then 1x 5ml for 8 min.) the resin is then washed with DMF (6x 5ml).

**Example 1.**

25 **1-(2-Amino-4-chlorobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**

4,4-Bipiperidine.dihydrochloride (4mmol,1g) was dissolved in water (5ml) and 2M sodium hydroxide solution (10mmol, 5ml) added. The solution was extracted with ethylacetate (2x 30 50ml) the combined extracts were washed with water, dried over anhydrous sodium carbonate, filtered and evaporated to give the 4,4 bipiperidine (0.35g) as a white solid. The 4,4

bipiperidine was dissolved in dry DMF (2ml) and added to Peg-tritylchloride resin (0.95 mmol/g, 1.5g) pre swollen in dry DCM (10ml). After 2h the resin was washed with DCM (6x5ml), DMF (6x5ml) and DCM (6x5ml). The resin was then air dried to allow aliquots to be taken.

The 4,4 bipiperidine trityl resin (0.1 mmol) was treated with Fmoc-D-Phenylglycine (0.5 mmol, 187mg), DMF(2.5ml), TBTU in DMF(1.25ml of a 450mM solution) and DIPEA in DMF (1.25ml of a 900 mM solution). The mixture was agitated with nitrogen for 2 hours. Deprotection and washing as above.

A solution of 4-chloroanthranilic acid (87mg 0.5mmole) in dry dimethylformamide (DMF) was treated successively with HOAt (102mg 0.75mmole) and EDCI (115mg 0.6mmole) and stirred at room temperature for 10min. The mixture was transferred to the reaction vessel on the Symphony and agitated for 2 hours with nitrogen. The resin was washed with DMF (6x5ml), DCM (6x5ml) and air dried. The product was cleaved from the resin with 10% triethylsilane in TFA (10ml) for 30 minutes, the resin filtered off and the TFA solution evaporated to dryness and triturated with diethyl ether to give the crude product. The crude product was dissolved in water (10ml), filtered and purified by preparative reverse phase Hplc.

25

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.30 (6H,m); 6.60 (1H,s); 6.55 (1H,d); 5.85 (1H, s); 4.40 (1H,m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 456 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.77 min.

30

**Example 2.****1-(2-Amino-5-bromobenzoyl-D-phenylglycanyl)-4',4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) 7.30 (7H, m); 6.50 (1H, d); 5.85 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m). MS TOF 500 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.31 min.

**Example 3.****1-(2-Amino-4-methylbenzoyl-D-phenylglycanyl)-4',4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) 7.30 (6H, m); 6.50 (1H, s); 6.45 (1H, d); 5.80 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.05 (3H, s); 1.60 (4H, m); 1.10 (6H, m). MS TOF 436 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.22 min.

**Example 4.****1-(2-Amino-5-methylbenzoyl-D-phenylglycanyl)-4',4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) 7.30 (7H, m); 6.50 (1H, d); 5.85 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m). MS TOF 436 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.74 min.

25

**Example 5.****1-(2-Amino-5-methoxybenzoyl-D-phenylglycanyl)-4',4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) 7.55 (6H, m); 7.30 (1H, d); 6.95 (1H, m); 6.15 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 3.60 (3H, s); 2.30-2.95 (6H, m); 2.20 (3H, s); 1.60 (4H, m); 1.10 (6H, m). MS TOF 452

(M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.20 min.

**Example 6.**

5 **1-(3-Methylbenzoyl-D-phenylglycinyl)-4,4'-bis(piperidine)**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.40 (2H, m); 7.30 (7H, m); 5.85 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.20 (3H, s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 421 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.68 min.

10

**Example 7.**

15 **1-(4-Methylbenzoyl-D-phenylglycinyl)-4,4'-bis(piperidine)**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.55 (2H, m); 7.30 (5H, m); 7.10 (2H, m); 5.85 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 2.20 (3H, s); 1.60 (4H, m); 1.10 (6H, m) MS TOF 420 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.61 min.

**Example 8.**

20 **1-(3-Amino-2-naphthoyl-D-phenylglycinyl)-4,4'-bis(piperidine)**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.90 (1H, d); 7.60 (1H, d); 7.40 (1H, m); 7.30 (6H, m); 7.05 (1H, m); 6.90 (1H, s); 5.85 (1H, s); 4.40 (1H, m); 3.75 (1H, m); 2.30-2.95 (6H, m); 1.60 (4H, m); 1.10 (6H, m) MS TOF 471 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.87 min.

25  
30 **Example 9.**  
**1-(3-Aminobenzoyl-D-phenylglycinyl)-4,4'-bis(piperidine)**  
MS TOF 421 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.06 min.

**Example 10.****1-(2-Aminobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**MS TOF 421 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 9.00 min.

5

**Example 11.****1-(2-Amino-4-fluorobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**MS TOF 440 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
10 water/acetonitrile/TFA) rt 9.23 min.**Example 12.****1-(2-Amino-5-fluorobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**15 MS TOF 440 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 9.14 min.**Example 13.****1-(2-Amino-4-nitrobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**20 MS TOF 467 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 10.59 min.**Example 14.****1-(2-Amino-5-nitrobenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**25 MS TOF ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 10.57 min.30 **Example 15.****1-(2-Amino-4,5-dimethoxybenzoyl-D-phenylglycanyl)-4,4'-bis(piperidine)**

MS TOF 481 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.67 min.

**Example 16.**

5 **1-(Benzoyl-D-phenylglycinyl)-4,4'-bispiperidine**

MS TOF 407 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.88 min.

**Example 17.**

10 **1-(4-Chlorobenzoyl-D-phenylglycinyl)-4,4'-bispiperidine**

MS TOF 441 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.89 min.

**Example 18.**

15 **1-(2-Hydroxybenzoyl-D-phenylglycinyl)-4,4'-bispiperidine**

MS TOF 423 ( $M+1^+$ ). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.97 min.

**Method 2:** By solution phase strategy: Typically an activated amino acid was treated with an amine (primary or secondary) or alcohol (1eq.). Activation of the protected amino acid (Boc or Cbz protection) was by HATU/DIPEA (1:2) by TBTU/DIPEA (1:2), by HOAt or HOAt and a carbodiimide (EDCI or DCC), or by diethyl cyanophosphonate and triethylamine or DIPEA, all couplings (minimum 120min.) were carried out in DMF without or with dichloromethane as co-solvent. After an aqueous work up the deprotection of the Boc group was achieved with TFA. Other acid substituents were added as the HOAt or HOAt esters either by activation with HBTU/HATU, EDC or DIPCI with or without Boc protection of amino groups. The final products were purified by preparative reverse phase Hplc.

**Examples 19-126**

The compounds of Examples 19-126 were prepared by the method described below, but using the appropriate starting materials.

Boc D-phenylglycine (251 mg, 1 mmol.) was dissolved in DMF (3ml) with HATU (380 mg., 1 mmol.) and DIPEA(350 $\mu$ l ., 2 mmol.). To this mixture was added 4-methylbenzylamine(121mg., 1 mmol.) and DIPEA (170 $\mu$ l., 1 mmol.). The mixture was stirred overnight. The mixture was then taken up into ethylacetate and washed with water, sodium carbonate solution, water, 10% hydrochloric acid solution and water. The ethylacetate was evaporated without drying and treated immediately with TFA for 30 min. The TFA was then evaporated to dryness and the product triturated with diethylether. TEA(1ml) was added and evaporated to dryness. A solution of 3-hydroxymethylbenzoic acid (76mg , 0.5mmole) in dry dimethylformamide (DMF) was treated with TBTU (161mg., 0.5mmol.) and DIPEA (1.5 mmol.). The mixture was then added to the D-phenylglycine-4-methylbenzylamide (0.5mmol.) and stirred overnight. The crude product was dissolved in water/acetonitrile (20ml), filtered and purified by preparative Hplc to yield pure product.

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.75 (1H, m); 7.65 (2H, m); 7.30 (7H, broad m); 6.80 (3H, m); 5.40 (1H, s); 4.45 (2H,s); 4.10 (2H, m); 2.10 (3H, s). MS TOF 389 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.51 min.

Compounds made by the above method:-

**Example 19.****1-(2-Aminobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (DMSO) 7.65 (3H, m); 7.45 (1H, m); 7.35 (5H, m); 7.15 (1H, m); 6.65 (1H, d); 6.55 (1H, m); 6.05 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 511 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.43 min.

**Example 20.****1-(2-Amino-4-chlorobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (DMSO) 7.55 (3H, m); 7.45 (1H, m); 7.35 (5H, m); 7.15 (1H, m); 6.75 (1H, s); 6.55 (1H, d); 6.05 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 546 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.18 min.

**Example 21.****1-(2-Amino-5-fluorobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CDCl<sub>3</sub>) 7.75 (1H, m); 7.60 (1H, m); 7.25 (6H, m); 7.15 (1H, m); 6.90 (1H, m); 6.75 (1H, m); 5.85 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 529 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.87 min.

**Example 22.****1-(2-Amino-4-methylbenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (DMSO) 7.55 (3H, m); 7.45 (2H, m); 7.35 (5H, m); 6.65 (1H, s); 6.35 (1H, d); 6.05 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m); 2.15 (3H, s);. MS TOF 525 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.12 min.

**Example 23.****1-(2-Amino-5-methylbenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CDCl<sub>3</sub>) 7.75 (1H, m); 7.60 (1H, m); 7.25 (6H, m); 7.15 (1H, m); 6.90 (1H, m); 6.75 (1H, m); 5.85 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m) 2.30 (3H, s). MS TOF 525 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.84 min.

10 **Example 24.****1-(2-Amino-4-nitrobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CDCl<sub>3</sub>) 7.75 (2H, m); 7.55 (1H, m); 7.35 (7H, m); 7.25 (1H, m); 5.80 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 556 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.35 min.

**Example 25.****1-(2-Amino-5-nitrobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CDCl<sub>3</sub>) 8.25 (1H, d); 7.85 (1H, m); 7.55 (1H, m); 7.25 (7H, m); 7.05 (1H, m); 5.80 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 556 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.08 min.

## 25

**Example 26.****1-(2-Amino-5-cyanobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.65 (4H, m); 7.25 (6H, m); 6.65 (1H, d); 5.80 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 536 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.89 min.

100

**Example 27.****1-(2,5-Diaminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

5      $^1\text{H}$  nmr ( $\text{CDCl}_3$ ) 7.70 (1H, d); 7.45 (7H, m); 6.85 (1H, s);  
6.55 (1H, m); 6.55 (1H, m); 5.90 (1H, s); 3.15 (3H, s); 3.00-  
2.00 (8H, m). MS TOF 526 ( $M+1^+$ ). Hplc (Magellan C8, Gradient  
3, water/acetonitrile/TFA) rt 11.82 min.

10   **Example 28.****1-(2-Amino-4,5-dimethoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15     $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 7.65 (2H, m); 7.35 (2H, m); 7.25 (5H, m);  
6.75 (1H, d); 6.15 (1H, d); 5.80 (1H, s); 3.60 (3H, s); 3.50  
15    (3H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 571 ( $M+1^+$ ).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
12.84 min.

**Example 29.**20   **1-(Benzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

20     $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 7.75 (2H, m); 7.70 (1H, m); 7.40 (10H, m);  
6.05 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 496  
( $M+1^+$ ). Hplc (Magellan C8, Gradient 3,  
25    water/acetonitrile/TFA) rt 12.84 min.

**Example 30.****1-(3-Aminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

30     $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 7.85 (1H, m); 7.60 (1H, m); 7.50 (2H, m);  
7.30 (7H, m); 7.05 (1H, d); 6.05 (1H, s); 3.15 (3H, s); 3.00-

2.00 (8H, m). MS TOF 511 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.32 min.

**Example 31.**

5 **1-(4-Aminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.95 (1H, d); 7.80-7.45 (10H, broad m); 7.35 (1H, d); 6.20 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 511 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, 10 water/acetonitrile/TFA) rt 12.05 min.

**Example 32.**

15 **1-(3,4 Diaminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.75 (1H, d); 7.40-7.15 (9H, broad m); 6.55 (1H, d); 6.00 (1H, s); 3.15 (3H, s); 3.00-2.00 (8H, m). MS TOF 540 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.30 min.

20 **Example 33.**

**1-(3-Chlorobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.85 (1H, m); 7.80 (1H, s); 7.60 (2H, m); 7.30 (8H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.00 (8H, m). 25 MS TOF 531 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.40 min.

**Example 34.**

**1-(4-Chlorobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.95 (1H, m); 7.75 (2H, m); 7.60 (1H, m); 7.40 (8H, m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.00 (8H, m).

MS TOF 531 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.54 min.

**Example 35.**

5 **1-(3-Amino-4-chlorobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CDCl<sub>3</sub>) 8.05 (1H, m); 7.80 (1H, m); 7.70 (1H, s); 7.20-7.60 (8H, broad m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.00 (8H, m). MS TOF 546 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 10 3, water/acetonitrile/TFA) rt 14.53 min.

**Example 36.**

**1-(4-Bromobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.85 (1H, m); 7.65 (2H, m); 7.60 (2H, d); 7.45 (2H, d); 7.30 (5H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.00 (8H, m). MS TOF 576 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.94 min.

20 **Example 37.**

**1-(4-Iodobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15 <sup>1</sup>H nmr (CD<sub>3</sub>CN)); 7.75 (2H, m); 7.65 (1H, m) 7.55 (2H, d); 7.45 (2H, d); 7.30 (5H, m); 5.95 (1H, s); 3.20 (3H, s); 3.00-25 2.00 (8H, m). MS TOF 622 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.96 min.

**Example 38.**

**1-(3-Amino-4-methylbenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-**

30 **methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.95 (1H, s); 7.60 (1H, d); 7.45 (1H, d); 7.40-7.15 (8H, broad m); 6.00 (1H, s); 3.15 (3H, s); 3.00-

2.50 (8H, m) 2.20 (3H, s). MS TOF 525 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.71 min.

**Example 39.**

5 **1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.85 (2H, d); 7.65 (1H, m); 7.50 (2H, m); 7.40 (5H, m); 6.80 (2H, d); 6.00 (1H, s); 3.80 (3H, s); 3.20 (3H, s); 3.00-2.00 (8H, m). MS TOF 526 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.63 min.

10

**Example 40.**

**1-(3-Amino-4-methoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15 <sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.90 (1H, m); 7.75 (1H, d); 7.60 (2H, m); 7.40-7.15 (6H, broad m); 7.45 (1H, d); 6.10 (1H, s); 3.95 (3H, s); 3.35 (3H, s); 3.00-2.50 (8H, m). MS TOF 541 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.78 min.

20

**Example 41.**

**1-(3,4-Dihydroxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

25 <sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.55 (1H, m); 7.45 (1H, d); 7.25 (2H, m); 7.15 (5H, m); 7.00 (1H, d); 6.60 (1H, d); 5.80 (1H, s); 3.05 (3H, s); 3.00-2.50 (8H, m). MS TOF 541 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.78 min.

**Example 42.**

30 **1-(Naphth-2-oyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 8.35 (1H, s); 8.00 (1H, d); 7.85 (5H, m); 7.45 (4H, m); 7.25 (4H, m); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 546 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.66 min.

5

**Example 43.****1-(3-Aminonaphth-2-oyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 8.15 (1H, d); 8.00 (1H, s); 7.75 (2H, m); 10 7.65 (1H, d); 7.30 7.60 (9H, m); 6.10 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 561 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.90 min.

**Example 44.****1-(Thiophene-3-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 8.15 (1H, s); 7.95 (1H, m); 7.85 (1H, m); 7.60 (8H, m); 6.30 (1H, s); 3.45 (3H, s); 2.00-2.50 (8H, m). MS TOF 502 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.28 min.

**Example 45.****1-(Thiophene-2-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.65 (2H, m); 7.45 (1H, s); 7.30 (2H, m); 7.20 (5H, m); 6.95 (1H, m); 6.00 (1H, s); 3.05 (3H, s); 3.00-2.50 (8H, m). MS TOF 502 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.52 min.

30 **Example 46.****1-(5-Methylthiophene-2-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CDCl<sub>3</sub>) 7.70 (1H, m); 7.45 (2H, m); 7.35 (6H, m); 6.65 (1H, m); 6.00 (1H, s); 3.05 (3H, s); 3.00-2.50 (8H, m) 2.45 (3H, s). MS TOF 516 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.98 min.

5

**Example 47.****1-(Isoquinolin-7-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 9.50 (1H, s); 8.75 (1H, s); 8.55 (1H, d); 10 8.30 (1H, d); 8.10 (2H, m); 7.65 (1H, m); 7.45 (2H, m); 7.35 (5H, m); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 547 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.39 min.

15 **Example 48.****1-(Pyridin-3-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 9.00 (1H, s); 8.70 (1H, d); 8.35 (1H, d); 8.10 (1H, m); 7.65 (2H, m); 7.45 (1H, m); 7.30 (5H, m); 6.00 20 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 497 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.99 min.

**Example 49.****1-(Indol-6-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.95 (2H, m); 7.60 (2H, m); 7.50 (3H, m); 7.35 (5H, m); 6.45 (1H, s); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 535 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.44 min.

**Example 50.**

**1-(2,5-Diaminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

MS TOF 526 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.89 min.

**Example 51.**

**1-(4-Methylaminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

10 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.65 (3H, m); 7.50 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m); 2.80 (3H, s). MS TOF 525 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.17 min.

15 **Example 52.**

**1-(3-Methyl-4-chlorobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

10 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.90 (1H, s); 7.85 (1H, s); 7.80 (1H, s); 7.55 (6H, m); 6.25 (1H, s); 3.45 (3H, s); 3.00-2.50 (8H, m); 2.60 (3H, s). MS TOF 545 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.39 min.

**Example 53.**

**1-(4-Vinylbenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

10 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.75 (2H, d); 7.60 (1H, m); 7.45 (4H, m); 7.35 (5H, m); 6.75 (1H, m); 6.05 (1H, s); 5.90 (1H, d); 5.30 (1H, d); 3.00-2.50 (8H, m); 2.80 (3H, s). MS TOF 522 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.45 min.

**Example 54.**

**1-(3-Amino-4-hydroxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.60 (1H, m); 7.50-7.10 (9H, m); 7.35 (1H, d); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 527 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 2, water/acetonitrile/TFA) rt 15.46 min.

**Example 55.**

**1-(4-Methylthiobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.85 (2H, d); 7.80 (1H, m); 7.60 (2H, m); 7.50 (5H, m); 7.40 (2H, d); 6.15 (1H, s); 3.40 (3H, s); 3.10-2.70 (8H, m); 2.60 (3H, s). MS TOF 542 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.67 min.

**Example 56.**

**1-(3-Carboxamidobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 8.25 (1H, s); 7.95 (2H, d); 7.70 (1H, m); 7.55 (3H, m); 7.40 (5H, m); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 539 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.83 min.

25

**Example 57.**

**1-(3-Amino-4-methylbenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.90 (1H, d); 7.70 (1H, m); 7.55 (2H, m); 7.45 (5H, m); 7.20 (1H, s); 6.95 (1H, d); 6.05 (1H, s); 3.80 (3H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 569 (M+1<sup>+</sup>).

Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
14.49 min.

**Example 58.**

5   **1-(3-Methyl-4-bromobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
 $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 7.65 (3H, m); 7.45 (3H, m); 7.30 (5H, m);  
6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m); 2.40 (3H, s).  
MS TOF 589 ( $\text{M}+1^+$ ). Hplc (Magellan C8, Gradient 3,  
10   water/acetonitrile/TFA) rt 16.67 min.

**Example 59.**

**1-(4-Ethoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15    $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 7.75 (2H, d); 7.60 (1H, m); 7.50 (2H, m);  
7.35 (5H, m); 6.85 (2H, d); 6.00 (1H, s); 4.00 (2H, m); 3.20  
(3H, s); 3.00-2.50 (8H, m); 1.30 (3H, t). MS TOF 540 ( $\text{M}+1^+$ ).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
16.58 min.

20

**Example 60.**

**1-(Indol-5-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1 $^1\text{H}$  nmr ( $\text{CD}_3\text{CN}$ ) 8.15 (1H, s); 7.95 (1H, m); 7.65 (2H, m);  
25   7.60-7.35 (7H, m); 6.60 (1H, s); 6.10 (1H, s); 3.30 (3H, s);  
3.00-2.60 (8H, m). MS TOF 535 ( $\text{M}+1^+$ ). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 13.88 min.

**Example 61.**

30   **1-(Benzimidazo-5-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 8.75 (1H, s); 8.25 (1H, s); 7.75 (2H, m); 7.60 (1H, m); 7.50 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 536 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 5 10.08 min.

**Example 62.****1-(3-Aminobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

10 <sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.65 (1H, m); 7.35 (5H, m); 7.05 (1H, m); 6.95 (2H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 435 (M+1<sup>+</sup>). Hplc (Magellan C8, 15 Gradient 3, water/acetonitrile/TFA) rt 7.65 min.

**Example 63.****1-(3-Amino-4-chlorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

20 <sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.30 (5H, m); 7.20 (1H, m); 6.95 (1H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 469 (M+1<sup>+</sup>). Hplc (Magellan C8, 25 Gradient 3, water/acetonitrile/TFA) rt 9.58 min.

**Example 64.****1-(3-Amino-4-methylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

30 <sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.35 (5H, m); 7.05 (2H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m);

2.65 (3H, s); 2.15 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 449 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 8.03 min

5 **Example 65.**

**1-(3-Aminonaphth-2-oyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.95 (1H, m); 7.65 (1H, d); 7.45 (2H, m); 7.30 (5H, m); 10 7.15 (1H, m); 6.95 (1H, s) 5.95 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 485 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.94 min.

15

**Example 66.**

**1-(Indol-6-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.78 (2H, s); 7.50 (1H, d); 7.25 (7H, m); 6.34 (1H, s); 20 6.82 (1H, s); 4.40 (1H, m); 3.83 (1H, m); 3.35 (2H, t); 2.9-2.4 (8H, m) and 2.65 (3H, s) masked by water in solvent; 1.60 (2H, m); 1.40 (2H, m); 1.08 (2H, m). MS TOF 459 (M+1<sup>+</sup>). Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA rt 10.01 25 min.

**Example 67.**

**1-(3-Amino-4-fluorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

30 <sup>1</sup>H nmr (d<sub>4</sub> methanol) a mixture of conformers only one recorded here 7.4 (6H, m); 7.1 (1H, m); 7.0 (1H, t); 6.0 (1H, s); 4.63 (1H, m); 4.02 (1H, m); 3.30 (2H, m); 2.90-2.40

(8H, m); 2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 453 (M+1<sup>+</sup>).

Hplc (Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 5.03 min.

5

**Example 68.**

**1-(3-Amino-4-bromobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.75 (1H, m); 7.35 (5H, m); 7.05 (1H, m); 6.80 (1H, m); 5.85 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m) and 2.65 (3H, s) masked by water in solvent; 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 513 and 515 (M+1<sup>+</sup>).

(Symmetry C8, Gradient 3, water/acetonitrile/TFA) rt 5.70 min.

**Example 69.**

**1-(3-Amino-4-methoxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.70 (1H, m); 7.30 (5H, m); 7.0 (2H, m); 6.72 (1H, d); 5.80 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.70 (3H, s); 3.30 (2H, m); 2.9-2.4 (8H, m) masked by water in solvent;

1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 465 (M+1<sup>+</sup>).

Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA) rt 7.55 min.

**Example 70.**

**1-(4-(Methylamino)benzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded here 7.70 (3H, m); 7.35 (5H, m); 6.60 (2H, d); 5.90 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.40 (2H, m); 2.9-2.4 (8H, m); 2.70 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m).  
5 MS TOF 465 (M+1<sup>+</sup>).

Hplc (Luna2 C18, Gradient 3, water/acetonitrile/TFA) rt 8.52 min.

**Example 71.**

10 **1-(4-Ethylaminobenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.65 (3H, m); 7.45 (2H, m); 7.35 (5H, m); 6.60 (2H, d); 6.00 (1H, s); 3.20 (3H, s); 3.10 (2H, q); 3.00-2.50 (8H, m); 1.15 (3H, t). MS TOF 539 (M+1<sup>+</sup>). Hplc  
15 (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.57 min.

**Example 72.**

1- (3-Methylaminobenzoyl-D-phenylglycinyl) -4- (4-fluoro-2-methylsulphonylphenyl)piperazine  
20 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.75 (1H, d); 7.60 (1H, d); 7.35 (7H, m); 7.15 (1H, t); 7.00 (1H, m); 6.70 (1H, d); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m); 2.70 (3H, s). MS TOF 525 (M+1<sup>+</sup>).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.07 min.  
25

**Example 73.**

1- (4-Chloro-3-aminobenzoyl-D-phenylglycinyl) -4- (2-methylsulphonylphenyl)piperazine  
30 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.95 (1H, d); 7.60 (1H, m); 7.45 (10H, m); 7.00 (1H, d); 6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 527 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.56 min.

**Example 74.**

**1-(4-Trifluoromethoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

5   <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.85 (3H, m); 7.65 (1H, d); 7.45 (2H, m);  
7.35 (6H, m); 6.00 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m).  
MS TOF 580 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 16.01 min.

10   **Example 75.**

**1-(4-Difluoromethoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.85 (3H, m); 7.45 (2H, d); 7.30 (5H, m);  
7.15 (2H, d); 6.80 (1H, t); 6.00 (1H, s); 3.20 (3H, s);  
15   3.00-2.50 (8H, m). MS TOF 562 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 14.99 min.

**Example 76.**

**1-(4-Trifluoromethylbenzoyl-D-phenylglycinyl)-N-(4-fluoro-2-methylsulphonylphenyl)piperazine**

20   1H nmr (CD<sub>3</sub>CN) 7.85 (2H, d); 7.70 (2H, d); 7.45 (2H, m);  
7.35 (6H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m).  
MS TOF 564 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 15.00 min.

25

**Example 77.**

**1-(Indol-3-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

30   1H nmr (CD<sub>3</sub>CN) 8.05 (1H, s); 7.85 (1H, d); 7.70 (1H, m); 7.50  
    (2H, m); 7.35 (6H, m); 7.20 (2H, m); 6.15 (1H, s); 3.20 (3H,  
    s); 3.00-2.50 (8H, m). MS TOF 535 (M+1+). Hplc (Magellan C8,  
    Gradient 3, water/acetonitrile/TFA) rt 14.25 min.

**Example 78.**

**1-(4-Chloro-3-aminobenzoyl-L-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

5    $^1\text{H}$  nmr (CD<sub>3</sub>CN) 7.75 (1H, d); 7.60 (1H, d); 7.45 (8H, m);  
6.90 (1H, d); 5.95 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m).  
MS TOF 545 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 14.53 min.

10   **Example 79.**

**1-(2-Carboxybenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.75 (1H, d); 7.60 (1H, d); 7.50 (1H, d);  
7.25-7.50 (9H, m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H,  
15   m). MS TOF 540 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 12.19 min.

**Example 80.**

**1-(2-Fluorobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

20   1H nmr (CD<sub>3</sub>CN) 7.85 (1H, m); 7.60 (1H, d); 7.25-7.50 (10H,  
m); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF  
514 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 13.29 min.

25

**Example 81.**

**1-(3-Bromoindol-6-carbonyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

30   1H nmr (CD<sub>3</sub>CN) 7.85 (2H, m); 7.70-7.20 (10H, m); 6.05 (1H,  
s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 614 (M+1+).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
16.16 min.

**Example 82.**

**1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

5    $^1\text{H}$  nmr (CD<sub>3</sub>CN) 7.95 (2H, m); 7.70-7.30 (10H, m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 570 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 16.18 min.

10   **Example 83.**

**1-(2-Cyanobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

15    $^1\text{H}$  nmr (CD<sub>3</sub>CN) 7.25-7.80 (12H, m); 6.05 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 521 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.85 min.

**Example 84.**

**1-(2-Aminomethylbenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

20    $^1\text{H}$  nmr (CD<sub>3</sub>CN) 7.95 (2H, m); 7.80-7.35 (10H, m); 6.15 (1H, s); 4.30 (2H, s); 3.15 (3H, s); 3.00-2.50 (8H, m). MS TOF 525 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.21 min.

25   **Example 85.**

**1-(4-Carboxy-3-aminobenzoyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

30    $^1\text{H}$  nmr (CD<sub>3</sub>CN) 7.75 (1H, d); 7.60 (1H, d); 7.45 (7H, m); 7.15 (1H, s); 6.85 (1H, d); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m). MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.00 min.

**Example 86.****1-(1H-Indazol-6-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 8.05 (2H, m); 7.85 (1H, d); 7.70 (1H, d); 7.55 (2H, m); 7.45 (5H, m); 5.95 (1H, s); 3.30 (3H, s); 3.00-2.50 (8H, m). MS TOF 545 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.44 min.

**Example 87.****1-(4-Methylcarboxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.95 (2H, m); 7.80 (2H, m); 7.45 (2H, m); 7.35 (6H, m); 6.00 (1H, s); 3.90 (3H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.90 min.

**Example 88.****1-(4-Acetoxybenzoyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.75 (3H, m); 7.60 (1H, d); 7.45 (2H, m); 7.35 (5H, m); 7.10 (2H, d); 6.00 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m); 2.20 (3H, s). MS TOF 554 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA)  
rt 14.53 min.

25

**Example 89.****1-(5-Methylpyrazin-2-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 8.90 (1H, s); 8.35 (1H, s); 7.55 (1H, m); 7.40 (2H, m); 7.25 (5H, m); 5.85 (1H, s); 3.10 (3H, s); 3.00-2.50 (8H, m); 2.40 (3H, s). MS TOF 512 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.17 min.

**Example 90.**

**1-(1,3-Benzodioxol-5-carbonyl-D-phenylglyciny1)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

5   <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.55 (2H, m); 7.35 (2H, m); 7.25 (6H, m);  
6.70 (1H, d); 5.85 (2H, s); 5.80 (1H, s); 3.10 (3H, s);  
3.00-2.50 (8H, m). MS TOF 540 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 14.28 min.

10   **Example 91.**

**1-(4-(Methylsulphonyl)benzoyl-D-phenylglyciny1)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.95 (3H, m); 7.60 (1H, m); 7.50 (2H, m); 7.35  
(6H, m); 6.05 (1H, s); 3.25 (3H, s); 3.10 (3H, s); 3.00-2.50  
15 (8H, m). MS TOF 574 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 13.62 min.

**Example 92.**

**1-(2,3-Dichloroindol-6-carbonyl-D-phenylglyciny1)-4-(4-fluoro-2-**

20   **methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.90 (1H, d); 7.85 (1H, s); 7.55 (2H, m); 7.40  
(2H, m); 7.25 (5H, m); 6.05 (1H, s); 3.30 (3H, s); 3.00-2.50  
(8H, m); 2.40 (3H, s). MS TOF 614 (M+1+). Hplc (Magellan  
C8, Gradient 3, water/acetonitrile/TFA)  
25   rt 16.35 min.

**Example 93.**

**1-(3-Chloro-2-oxo-(1H)indol-6-carbonyl-D-phenylglyciny1)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

30   1H nmr (CD<sub>3</sub>CN) 7.90 (1H, d); 7.55 (1H, m); 7.25-7.50 (9H, m);  
5.95 (1H, s); 5.20 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m).

MS TOF 585 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.38 min.

**Example 94.**

5 **1-(3,3-Dichloro-2-oxo-(1H)indol-6-carbonyl-D-phenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)-piperazine**  
1H nmr (CD3CN) 7.90 (1H, d); 7.65 (2H, m); 7.55 (1H, m); 7.45  
(2H, m); 7.35 (5H, m); 5.95 (1H, s); 3.25 (3H, s); 3.00-2.50  
(8H, m). MS TOF 619 (M+1+). Hplc (Magellan C8, Gradient 3,  
10 water/acetonitrile/TFA) rt 15.13 min.

**Example 95.**

1-**(3-Methylindol-6-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**  
15 1H nmr (CD3CN) a mixture of conformers only one recorded  
here 7.85 (2H, m); 7.40 (3H, m); 7.30 (3H, m); 7.05 (1H, s);  
5.95 (1H, s); 4.55 (1H, m); 3.85 (1H, m); 3.30 (2H, m);  
2.90-2.40 (8H, m); 2.55 (3H, s); 2.20 (3H, s); 1.60 (2H, m);  
1.30 (2H, m); 1.00 (2H, m). MS TOF 473 (M+1+). Hplc  
20 (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.40  
min.

**Example 96.**

1-**(2,3-Dihydroindol-6-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**  
25 1H nmr (CD3CN) a mixture of conformers only one recorded  
here 7.75 (1H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m);  
3.85 (1H, m); 3.65 (2H, t); 3.30 (2H, m); 3.10 (2H, t);  
2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30 (2H, m);  
30 1.00 (2H, m). MS TOF 461 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 8.68 min.

**Example 97.****1-(1H-indazol-6-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded  
here 7.95 (1H, m); 7.85 (2H, m); 7.65 (1H, m); 7.45 (2H, m);  
7.30 (3H, m); 5.95 (1H, s); 4.55 (1H, m); 3.95 (1H, m); 3.30  
(2H, m); 2.90-2.40 (8H, m); 2.55 (3H, s); 1.60 (2H, m); 1.30  
(2H, m); 1.00 (2H, m). MS TOF 460 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 9.72 min.

10

**Example 98.****1-(Benzimidazol-5-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded  
here. 8.05 (1H, s); 7.90 (1H, m); 7.75 (2H, m); 7.30 (5H, m);  
5.95 (1H, s); 4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m);  
2.90-2.40 (8H, m); 2.75 (3H, s); 1.60 (2H, m); 1.30 (2H, m);  
1.00 (2H, m). MS TOF 460 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 8.80 min.

20

**Example 99.****1-(Benzthiazol-6-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded  
here 8.40 (1H, s); 7.95 (3H, m); 7.30 (5H, m); 5.85 (1H, s);  
4.45 (1H, m); 3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m);  
2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS  
TOF 477 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 9.58 min.

30

120

**Example 100.****1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD3CN) a mixture of conformers only one recorded  
here 7.85 (2H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m);  
3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s);  
1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 493 (M+1+).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
12.22 min.

10

**Example 101.****1-(3-Bromoindol-6-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD3CN) a mixture of conformers only one recorded  
here 7.85 (2H, m); 7.30 (7H, m); 5.85 (1H, s); 4.45 (1H, m);  
3.85 (1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s);  
1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 539 (M+1+).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
12.45min.

20

**Example 102.****1-(3-Amino-4-chlorobenzoyl-L-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CDCl3) a mixture of conformers only one recorded  
here 7.65 (1H, m); 7.30 (6H, m); 7.00 (1H, m); 5.85 (1H, s);  
4.65 (1H, m); 3.80 (1H, m); 3.55 (2H, m); 2.90-2.40 (8H, m);  
2.65 (3H, s); 1.60 (2H, m); 1.30 (2H, m); 1.00 (2H, m). MS  
TOF 469 (M+1+). Hplc (Magellan C8, Gradient 3,  
water/acetonitrile/TFA) rt 10.71min.

30

**Example 103.****1-(4-Vinylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1H nmr (CD<sub>3</sub>CN) a mixture of conformers only one recorded  
here 7.85 (1H, m); 7.70 (2H, m); 7.40 (6H, m); 6.75 (1H, m);  
6.00 (1H, s); 5.85 (1H, d); 5.50 (1H, d); 4.55 (1H, m); 3.95  
(1H, m); 3.30 (2H, m); 2.90-2.40 (8H, m); 2.65 (3H, s); 1.60  
(2H, m); 1.30 (2H, m); 1.00 (2H, m). MS TOF 446 (M+1+).  
Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt  
11.21min.

**Example 104.****1-(3-Amino-4-chlorobenzoyl-D-phenylglycinyl)-4-(4-amino-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.55 (1H, m); 7.45 (3H, m); 7.35 (5H, m);  
7.10 (1H, d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s);  
3.00-2.50 (8H, m). MS TOF 542 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 12.02 min.

**Example 105.****1-(3-Aminobenzoyl-D-phenylglycinyl)-4-(4-amino-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.55 (2H, m); 7.45 (3H, m); 7.35 (5H, m);  
7.10 (1H, d); 6.90 (1H, d); 6.10 (1H, s); 3.10 (3H, s);  
3.00-2.50 (8H, m). MS TOF 508 (M+1+). Hplc (Magellan C8,  
Gradient 3, water/acetonitrile/TFA) rt 9.35 min.

**Example 106.****1-(3-Amino-4-chlorobenzoyl-D-phenylglycinyl)-4-(4-carboxamido-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 8.05 (1H, d); 7.80 (1H, m); 7.35-7.60 (8H, m);  
7.10 (1H, d); 6.10 (1H, s); 3.25 (3H, s); 3.00-2.50 (8H, m).

MS TOF 570 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.24 min.

**Example 107.**

5 **1-(3-Amino-4-chlorobenzoyl-D-phenylglycinyl)-4-(4-nitro-2-methylsulphonylphenyl)piperazine**  
1H nmr (CD3CN) 8.70 (1H, s); 8.45 (1H, d); 7.55 (1H, m); 7.45 (5H, m); 7.30 (2H, m); 7.10 (1H, d); 6.10 (1H, s); 3.40 (3H, s); 3.00-2.50 (8H, m). MS TOF 572 (M+1+). Hplc (Magellan  
10 C8, Gradient 3, water/acetonitrile/TFA) rt 14.25 min.

**Example 108.**

15 **1-(3-Amino-4-chlorobenzoyl-D-4-aminophenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
1H nmr (CD3CN) 7.65 (1H, d); 7.45 (4H, m); 7.25 (2H, m); 7.15 (2H, d); 7.05 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 560 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.90 min.

20 **Example 109.**

20 **1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**  
1H nmr (CD3CN) 7.70 (2H, d); 7.55 (1H, d); 7.45 (2H, d); 7.25 (2H, m); 7.20 (2H, d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 3.00-2.50 (8H, m). MS TOF 588 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.18 min.

**Example 110.**

30 **1-(3-Amino-4-chlorobenzoyl-D-4-(methylcarboxamido)phenyl-glycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

1H nmr (CD<sub>3</sub>CN) 7.70 (2H, d); 7.55 (1H, d); 7.45 (2H, d); 7.25 (2H, m); 7.20 (2H, d); 6.90 (1H, d); 6.10 (1H, s); 3.20 (3H, s); 2.70 (3H, s); 3.00-2.50 (8H, m). MS TOF 602 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 5 12.70 min.

**Example 111.**

**3-Amino-4-chlorobenzoyl-D-phenylglycine 4-methylbenzylamide**  
1H nmr (CD<sub>3</sub>CN) 7.55 (1H, m); 7.35 (7H, m); 7.00 (4H, m); 5.45 10 (1H, s); 4.25 (2H, m); 2.20 (3H, s). MS TOF 408 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.61 min.

**Example 112.**

15 **3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine R,S -2-methylcyclohexylamide**  
1H nmr (CD<sub>3</sub>CN) mixture of isomers only one recorded here  
7.75 (2H, d); 7.60 (2H, m); 7.30 (2H, m); 7.10 (1H, d); 5.55 (1H, s); 3.90 (1H, m); 3.25 (1H, m); 1.00-2.00 (8H, m) 0.50 20 (3H, m). MS TOF 443 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 9.18 min

**Example 113.**

25 **3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine 2-indanamide**  
MS TOF 463 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.58 min.

**Example 114.**

30 **3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine (S)-N-benzyl-alpha-methylbenzylamide**

MS TOF 541 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 15.34 min.

**Example 115.**

5 **3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine 1-(S)-1-naphthylethylamide**

MS TOF 5013 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.00 min.

10 **Example 116.**

**3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycine 3-(1-(R,S)-hydroxyethyl)benzamide**

MS TOF 443 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.81 min.

15

**Example 117.**

**3-Amino-4-chlorobenzoyl-D-phenylglycine cis,trans-2-aminocyclohexylamide**

20 MS TOF 401 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.00 min.

}

**Example 118.**

**1-(3-Amino-4-chlorobenzoyl-D,L-(4-piperidinyl)glycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

25 MS TOF 552 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.00 min.

**Example 119.**

30 **1-(3-Amino-4-chlorobenzoyl-D,L-(4-N-methylpiperidinyl)-glycinyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

MS TOF 566 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.83 min.

**Example 120.**

1-(3-Amino-4-chlorobenzoyl-D,L-(4-N-trifluoroacetyl-piperidinyl)glycinyl-4-(4-fluoro-2-methylsulphonylphenyl)-5-piperazine

MS TOF 649 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.63 min.

**Example 121.**

10 3-Amino-4-chlorobenzoyl-D-phenylglycine (2-chloro-5-carboxamido)benzenesulphonamide

MS TOF 521 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.23 min.

**Example 122.**

1- (4-Cyanobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine

MS TOF 445 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.13min.

20

**Example 123.**

1- (3-Cyanobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine

MS TOF 445 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 10.23min.

**Example 124.**

1-(4-Chlorobenzoyl-D-phenylglycinyl)-4-(4-pyridyl)-piperazine

MS TOF 435 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.11 min.

30

**Example 125.**

**1-(4-Methoxybenzyl-D-phenylglycanyl)-4-(4-fluoro-2-methylsulphonylphenyl)piperazine**

MS TOF 512 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 11.91 min.

**Example 126.**

**1-N-(3-Amino-4-chlorobenzoyl)-2-N-(4-methoxybenzoyl)-1,2-diamino-1-phenylethane**

1H nmr (CD3OH) 7.45 (2H, m); 7.35 (3H, m); 7.20 (2H, m); 7.10 (3H, m); 6.75 (2H, d); 4.80 (1H, m); 4.25 (2H, m); 3.70 (3H, s). MS TOF 424 (M+1+). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 14.05 min.

15 **Examples 127 to 136.**

**Preparation of Starting Materials**

**4-methoxybenzoyl-D-phenylglycanyl-R,S-3-hydroxypyrrolidine**

D-phenylglycanyl-R,S-3-hydroxypyrrolidine (3.42g, 15.5mmol)

20 was dissolved in dichloromethane (100ml) and placed under argon. Triethylamine (2.27ml, 16.28mmol) was added followed by 4-methoxybenzoyl chloride (2.78g, 16.3mmol) and the mixture stirred at room temperature for 3.5h. The organic solution was washed with 0.5% hydrochloric acid (50ml), sat. sodium bicarbonate solution (50ml) and brine (50ml). The organic solution was dried ( $MgSO_4$ ) and evaporated to an off-white solid, 4-methoxybenzoyl-D-phenylglycanyl-R,S-3-hydroxypyrrolidine, (5.49g, 100%)

Hplc (Luna C18, Gradient 3, water/acetonitrile/TFA), rt,

30 11.7min

LCMS M+1 355 Nmr.

**4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine**

By a similar method D-phenylglycanyl-4-hydroxypiperidine was converted to 4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine.

5 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,

11.9min

LCMS M+1 369 Nmr

**Example 127**

10 **1-(4-Methoxybenzoyl-D-phenylglycyl)-3-(R,S)-(2-fluorophenoxy)pyrrolidine**

To a solution of 4-methoxybenzoyl-D-phenylglycyl-R,S-3-hydroxypyrrolidine (400mg, 1.13mmol) in benzene (10ml) at 10°C was added 2-triphenylphosphonium 4,4-dimethyl-

15 tetrahydro-1,2,5-thiadiazolidine 1,1-dioxide (Reference: J. Castro et al. J. Org. Chem. 1994, 59, 2289-2291) (696mg, 1.69mmol) and 3-methoxyphenol (210mg) and the mixture allowed to warm to room temperature overnight. The reaction mixture was diluted with ether (30ml) and washed with dilute 20 sodium bicarbonate solution. The organic solution was dried ( $MgSO_4$ ) and concentrated. The residue was purified by reverse phase preparative chromatography to give 1-(4-methoxybenzoyl-D-phenylglycyl)-3-(R,S)-(3-methoxyphenoxy)pyrrolidine.

25 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 11.75min.

LCMS M+1 461 Nmr (mixture of diastereomers).

**Example 128.**

30 **1-(4-Methoxybenzoyl-D-phenylglycyl)-3-(R,S)-(3-methoxyphenoxy)pyrrolidine**

From 4-methoxybenzoyl-D-phenylglycinyl-R, S-3-hydroxypyrrolidine and 3-methoxyphenol:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 11.75min.

5 LCMS M+1 461 Nmr (mixture of diastereomers).

**Example 129.**

**1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(3-methoxyphenoxy)piperidine**

10 From 4-methoxybenzoyl-D-phenylglycinyl-4-hydroxypiperidine and 3-methoxyphenol:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 16.09min

LCMS M+1 475. Nmr

15

**Example 130.**

**1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(4-methoxyphenoxy)piperidine**

From 4-methoxybenzoyl-D-phenylglycinyl-4-hydroxypiperidine and 4-methoxyphenol:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 15.8min.

LCMS M+1 475. Nmr.

25 **Example 131.**

**1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(3-fluorophenoxy)piperidine**

From 4-methoxybenzoyl-D-phenylglycinyl-4-hydroxypiperidine and 3-fluorophenol:

30 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 12.75min.

LCMS M+1 463 Nmr

**Example 132.**

**1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(2-methanesulfonylphenoxy)piperidine**

5 From 4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine and 2-methanesulphonylphenol:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
10.8min.

LCMS M+1 523 Nmr.

10

**Example 133.**

**1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(2-methylmercaptophenoxy)piperidine**

From 4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine  
15 and 2-methylmercaptophenol:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
12.7min

LCMS M+1 491 Nmr.

20

**Example 134.**

**1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(2-fluoro-phenoxy)piperidine**

From 4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine and 2-fluorophenol:

25 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
15.8min.

LCMS M+1 463 Nmr.

**Example 135.**

30 **1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(phenoxy)piperidine**  
From 4-methoxybenzoyl-D-phenylglycanyl-4-hydroxypiperidine and phenol:

130

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
16.8min.

LCMS M+1 445

5 **Example 136.**

**1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(3-pyridoxy)piperidine**

From 4-methoxybenzoyl-D-phenylglycinyl-4-hydroxypiperidine  
and 3-hydroxypyridine:

10 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
11.4min

LCMS M+1 446 Nmr

**Example 137.**

**1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(4-fluorophenoxy)piperidine**

To a solution of triphenylphosphine (285mg, 1.09mmol) in dry THF (5ml) under argon at -15°C was added slowly (<-10°C) diethyl azodicarboxylate (DEAD) (208mg, 1.19mmol) and the 20 solution stirred at <-10°C for 5min. To this mixture was added a solution of 4-methoxybenzoyl-D-phenylglycinyl-4-hydroxypiperidine (400mg, 1.08mmol) and 4-fluorophenol (122mg, 1.09mmol) in dry THF (5ml) over 5min at <-10°C. The reaction was warmed to room temperature and monitored by tlc (SiO<sub>2</sub> - ethyl acetate). The reaction mixture was poured into water (5ml) and extracted with dichloromethane (100ml). The organic solution was washed with sat. sodium bicarbonate (50ml) and 0.5% hydrochloric acid (50ml), dried (MgSO<sub>4</sub>) and concentrated and the residue purified by flash chromatography, (SiO<sub>2</sub> - 30% ethyl acetate in hexane to give 30 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(4-fluorophenoxy)piperidine, (107mg, 21%)

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
16.0min  
LCMS M+1 463. Nmr.

5 Examples 138 to 142

Preparation of Starting Materials

**Benzylloxycarbonyl-D-phenylglycinyl-R,S-3-hydroxypyrrolidine**

Benzylloxycarbonyl-D-phenylglycine (18.01g, 63.1mmol) and

10 R,S-3-hydroxypyrrolidinol (5.0g, 57.4mmol) were suspended in dimethylformamide (300ml). HOAt (8.61g, 63.1mmol) was added, the mixture stirred for 3min. and then EDCI (12.1g 63.1mmol) was added with stirring and the mixture left overnight. The orange solution was concentrated *in vacuo* and the residue taken up in ethyl acetate (300ml). The organic solution was washed with sat. sodium bicarbonate (2 x 100ml), 0.5% aqueous hydrochloric acid (50ml) and brine (100ml). The organic solution was dried ( $MgSO_4$ ) and evaporated *in vacuo* to give an orange solid. Flash chromatography ( $SiO_2$  1:1 dichloromethane: ethyl acetate gave benzylloxycarbonyl-D-phenylglycinyl-R,S-3-hydroxypyrrolidine, (11.4g, 56%).  
Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 12.7min  
LCMS M+1 355 Nmr.

25

**Benzylloxycarbonyl-D-phenylglycinyl-4-hydroxypiperidine**

By a similar method using benzylloxycarbonyl-D-phenylglycine and 4-hydroxypiperidine, benzylloxycarbonyl-D-phenylglycinyl-4-hydroxypiperidine was prepared.

30 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 11.9min  
LCMS M+1 369 Nmr.

**D-Phenylglycinyl-R,S-3-hydroxypyrrolidine**

Benzylloxycarbonyl-D-phenylglycinyl-R,S-3-hydroxypyrrolidine, (5.49g, 15.5mmol) was dissolved in ethanol (120ml) and Pd/C (10%, 100mg) added. The mixture was hydrogenated at atmospheric pressure until complete by tlc ( $\text{SiO}_2$  ethyl acetate - starting material Rf. 0.6, product 0.05). The catalyst was filtered off through celite and concentrated *in vacuo* to give D-phenylglycinyl-R,S-3-hydroxypyrrolidine as a yellow oil, (3.54g, 16.1mmol).

**D-Phenylglycinyl-4-hydroxypiperidine**

By a similar method benzylloxycarbonyl-D-phenylglycinyl-4-hydroxypiperidine was converted to D-phenylglycinyl-4-hydroxypiperidine

**Benzylloxycarbonyl-D-phenylglycinyl-4-(3-pyridoxy)piperidine**

To a solution of benzylloxycarbonyl-D-phenylglycinyl-4-hydroxypiperidine (500mg, 1.36mmol), 3-hydroxypyridine (129mg, 1.36mmol) and triphenylphosphine (356mg, 1.36mmol) in dry THF (20ml) at 0°C, was slowly added diethyl azodicarboxylate (259mg, 1.19mmol) and the mixture stirred for 1h at 0°C and then 16h at room temperature. Water (5ml) was added and the mixture extracted with ethyl acetate (2 x 10ml). The organic solution was washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated to an oil which was purified by flash chromatography, ( $\text{SiO}_2$  - hexane/ethyl acetate 1:1) to give benzylloxycarbonyl-D-phenylglycinyl-4-(3-pyridoxy)piperidine, (490mg 65% - contaminated with triphenylphosphine)

**Benzylloxycarbonyl-D-phenylglycanyl-R,S-3-(3-pyridoxy)-pyrrolidine**

A solution of benzylloxycarbonyl-D-phenylglycanyl-R,S-3-hydroxypyrrolidine (2.0g, 8.64mmol), 2-triphenylphosphonium 5 4,4-dimethyl-tetrahydro-1,2,5-thiadiazolidine 1,1-dioxide (Reference: J. Castro et al. J. Org. Chem. 1994, 59, 2289-2291) (3.479g, 8.47mmol) and 3-hydroxypyridine (0.805g, 8.47mmol) in benzene (30ml) was stirred at room temperature for 18h. The mixture was poured onto ether (50ml) and the 10 organic solution was washed with sat. sodium bicarbonate (2 x 50ml). The product was extracted into 5% hydrochloric acid which was then basified (pH8) with 2M sodium hydroxide solution and extracted with ether (3 x 100ml). The organic solution was dried ( $MgSO_4$ ) and evaporated to give 15 benzylloxycarbonyl-D-phenylglycanyl-R,S-3-(3-pyridoxy)pyrrolidine

**D-Phenylglycanyl-4-(3-pyridoxy)piperidine**

Benzylloxycarbonyl-D-phenylglycanyl-4-(3-pyridoxy)piperidine 20 (1.18g 2.64mmol) was dissolved in ethanol (120ml) containing Pd/C 10% (100mg) and acetic acid (0.3ml) and hydrogenated at atmospheric pressure for 8h - (incomplete by tlc). The catalyst was removed by filtration and the solution evaporated to an oil. The oil was re-hydrogenated as before. 25 The catalyst was removed by filtration and the solvent evaporated *in vacuo* to an oil which was taken up in dilute hydrochloric acid. The aqueous solution was washed with dichloromethane and then basified with solid sodium bicarbonate. Extraction with chloroform, drying ( $MgSO_4$ ) and 30 evaporation of the solvent *in vacuo* gave D-phenylglycanyl-4-(3-pyridoxy)piperidine, (331mg 40%). Nmr

**D-phenylglycanyl-R,S-3-(3-pyridoxy)pyrrolidine**

In a similar manner D-phenylglycanyl-R,S-3-(3-pyridoxy)pyrrolidine was prepared from benzyloxycarbonyl-D-phenylglycanyl-R,S-3-(3-pyridoxy)pyrrolidine by

5 hydrogenation over Pd/C in ethanol. Nmr.

**Example 138.****1-(Indole-6-carbonyl-D-phenylglycanyl)-4-(3-pyridoxy)piperidine**

10 A mixture of EDCI (169mg 0.88mmol), HOAt (120mg 0.88mmol) and indole-6-carboxylic acid (142mg 0.88mmol) in DMF (5ml) was stirred for 2min and then added to a solution of D-phenylglycanyl-4-(3-pyridoxy)piperidine (229mg 0.735mmol) and triethylamine (89mg 0.88mmol) in DMF (20ml). The mixture  
15 was stirred at room temperature for 3h and excess solvent removed *in vacuo*. The residue was taken up in ethyl acetate (150ml) and washed with sat. sodium bicarbonate (50ml). The solution was dried ( $MgSO_4$ ), evaporated and the residue purified by flash chromatography ( $SiO_2$  ethyl acetate:  
20 methanol 0% - 5%) to give 1-(indole-6-carbonyl-D-phenylglycanyl)-4-(3-pyridoxy)piperidine (122mg 41%)  
Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
10.8min.

LCMS M+1 455 Nmr

25

The following were prepared in a similar manner:

**Example 139.****1-(3-Chloroindole-6-carbonyl-D-phenylglycanyl)-4-(3-**

30 **pyridoxy)piperidine**

From D-phenylglycanyl-4-(3-pyridoxy)piperidine and 3-chloro-6-indolecarboxylic acid:

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt  
11.95min

LMCS M+1 489 Nmr

5 **Example 140.**

**1-(Indole-6-carbonyl-D-phenylglycinyl)-3-(R,S)-(3-pyridoxy)pyrrolidine**

From D-phenylglycinyl-R,S-3-(3-pyridoxy)pyrrolidine and 6-indolecarboxylic acid.

10 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
6.4min.

LCMS M+1 441 Nmr (mixture of diastereomers).

**Example 141.**

15 **1-(3-Chloroindole-6-carbonyl-D-phenylglycinyl)-3-(R,S)-(3-pyridoxy)pyrrolidine**

From D-phenylglycinyl-R,S-3-(3-pyridoxy)pyrrolidine and 3-chloro-6-indolecarboxylic acid.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
20 7.2min.

LCMS M+1 475 Nmr (mixture of diastereomers).

**Example 142.**

25 **1-(3-Methylindole-6-carbonyl-D-phenylglycinyl)-3-(R,S)-(3-pyridoxy)pyrrolidine**

From D-phenylglycinyl-R,S-3-(3-pyridoxy)pyrrolidine and 3-methyl-6-indolecarboxylic acid.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 6.84  
and 7.0min.

30 LCMS M+1 455 Nmr (mixture of diastereomers).

**Example 143.**

(R)-2-(1'-(3-Chloroindole-6-carboxamido)benzyl)-4-methoxyphenyl-1,3-thiazole

5 (R)-2-(1'-benzyloxycarbonylamidobenzyl)-4-methoxyphenyl-1,3-thiazole

To a solution of benzyloxycarbonyl-D-phenylglycine thioamide (1g, 3.33mmol.) in acetone (25ml) was added  $\alpha$ -bromo-4-methoxyacetophenone (0.76g, 3.32mmol) and the mixture 10 stirred at room temperature for 30min. Chloroform (25ml) and sat. aqueous sodium hydrogen carbonate (30ml) were added and the organic solution separated, dried ( $MgSO_4$ ) and evaporated *in vacuo*. The residue was dissolved in dichloromethane (30ml) and pyridine (0.5ml, 6.18mmol) and 15 trifluoroacetic anhydride (0.5ml, 3.54mmol) were added. The mixture was stirred at room temperature until complete by tlc ( $SiO_2$  dichloromethane - 1h.), washed with 5% hydrochloric acid, dried ( $MgSO_4$ ) and evaporated *in vacuo*. Flash chromatography of the residue (0.87g). ( $SiO_2$  - 20 dichloromethane) gave (R)-2-(1'-benzyloxycarbonylamidobenzyl)-4-methoxyphenyl-1,3-thiazole (0.74g 1.72mmol. 52%)

Nmr:  $CDCl_3$  7.85 (2H, d), 7.3-7.5 (11H, m), 6.95 (2H, d), 6.44 (0.5H, bd), 6.16 (0.5H, bd), 5.02-5.22 (2H, m), 3.83 (3H. m).

25

(R)-2-(1'-aminobenzyl)-4-methoxyphenyl-1,3-thiazole

(R)-2-(1'-Benzylloxycarbonylamidobenzyl)-4-methoxyphenyl-1,3-thiazole (0.70g, 1.63mmol) was dissolved in acetic acid (50ml) and HBr in acetic acid (25ml) added. The mixture was 30 heated in a 50°C oil bath for 2h when no starting material remained by tlc ( $SiO_2$  30% ether in dichloromethane). The

mixture was evaporated *in vacuo*, basified with sat. aqueous sodium hydrogen carbonate and extracted with ethyl acetate (x3). The organic solution was dried ( $MgSO_4$ ) and evaporated *in vacuo*. Flash chromatography ( $SiO_2$  dichloromethane then 5 30% ether in dichloromethane) gave (R)-2-(1'-aminobenzyl)-4-methoxyphenyl-1,3-thiazole (172mg, 36%)

Nmr:  $CDCl_3$  7.7 (2H, d), 7.5 (2H, d), 7.17-7.4 (3H, m), 6.85 (2H, d), 3.76 (3H, s)

(R)-2-(1'-(3-Chloroindole-6-carboxamido)benzyl)-4-methoxyphenyl-1,3-thiazole  
10

(R)-2-(1'-Aminobenzyl)-4-methoxyphenyl-1,3-thiazole (80mg, 0.27mmol) was coupled to 3-chloroindolecarboxylic acid using EDC/HOAt to give: (R)-2-(1'-(3-Chloroindole-6-carboxamido)benzyl)-4-methoxyphenyl-1,3-thiazole (49%)  
15 Hplc (Luna C18 Gradient3) rt 17.2min.  
LCMS M+1 474. Nmr.

**Examples 144 to 147.**

20 The compounds of Examples 144 to 147 were prepared by coupling to the appropriate carboxylic acid to D-phenylglycinyl-4,4'-(1'-methylbispiperidine) using EDC and HOAt as described previously.

25 **Example 144.**

**1-(4-Methylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

Hplc (Luna C18 Gradient3) rt 11.2min.  
LCMS M+1 434. Nmr.

**Example 145.**

**1-(4-Chlorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

Hplc (Luna C18 Gradient3) rt 11.5min.

5 LCMS M+1 454. Nmr.

**Example 146.**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

10 Hplc (Luna C18 Gradient3) rt 11.1min.

LCMS M+1 450. Nmr.

**Example 147**

**1-(3,4-Methylenedioxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

15 Hplc (Luna C18 Gradient3) rt 10.65min.

LCMS M+1 464. Nmr.

**Example 148.**

20 **1-(Indole-6-carbonyl-D-phenylglycinyl)-1'-isopropyl-4,4'-bis(piperidine)**

**Benzylloxycarbonyl-D-phenylglycinyl-4,4'-(1'-bis(piperidine))**

25 **Benzylloxycarbonyl-D-phenylglycinyl- 1'-isopropyl-4,4'-bis(piperidine)**

**D-phenylglycinyl-1'-isopropyl-4,4'-bis(piperidine)**

30 **1-(Indole-6-carbonyl-D-phenylglycinyl)- 1'-isopropyl-4,4'-bis(piperidine)**

Prepared by coupling the appropriate carboxylic acid to D-phenylglycinyl-4,4'-(1'-(2''-propyl)bispiperidine).

Hplc (Luna C18 Gradient3) rt 11.46min.

LCMS M+1 487. Nmr.

5

**Examples 149 to 154.**

The compounds of Examples 149 to 154 were prepared by coupling Boc-D-4-carboxamidophenylglycine to the appropriate amine with EDCI/HOAt, deprotection with TFA/DCM and coupling to 3-amino-4-chlorobenzoic acid with EDCI/HOAt as previously described.

**Example 149.**

15 **2-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycinyl)-1,2,3,4-tetrahydroisoquinoline**

Hplc (Luna C18 Gradient3) rt 13.15min.

LCMS M+1 463. Nmr.

20 **Example 150.**

**1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenyl-glycinyl)-4-benzylpiperazine**

Hplc (Luna C18 Gradient3) rt 11.4min.

LCMS M+1 512. Nmr.

25

**Example 151.**

**1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenylglycinyl)-4-(2-methylthiophenyl)piperazine**

Hplc (Luna C18 Gradient3) rt 14.3min.

30 LCMS M+1 539. Nmr.

**Example 152.**

**1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenyl-glyciny)-4-(2-phenylethyl)piperazine**

Hplc (Luna C18 Gradient3) rt 11.1min.

5 LCMS M+1 521. Nmr.

**Example 153.**

**1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenyl-glyciny)-4-benzoylpiperidine**

10 Hplc (Luna C18 Gradient3) rt 12.8min.

LCMS M+1 520. Nmr.

**Example 154.**

**1-(3-Amino-4-chlorobenzoyl-D-4-carboxamidophenyl-glyciny)-4-(2-ethylphenyl)piperazine**

Hplc (Luna C18 Gradient3) rt 13.9min.

LCMS M+1 521. Nmr.

**Example 155.**

20 **1-(3-Methoxyindole-6-carbonyl-D-phenylglyciny)-1'-methyl-4',4'-bis(piperidine)**

**Methyl 1-acetyl-3-formylindole-6-carboxylate**

A suspension of methyl 3-formylindole-6-carboxylate (1g, 25 4.93 mmol) in acetic anhydride (10ml) was refluxed for 2 h. The acetic anhydride was removed under reduced pressure to afford a pinkish solid (1.2g, 100%) that was used without further purification.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 2.7 (3H, s), 3.9 (3H, s), 8.05 (1H, d), 8.15 (1H, s), 8.25 (1H, d), 9.0 (1H, s), 30 10.1 (1H, s); LCMS M+H 246.

**Methyl 1-acetyl-2,3-dihydroindol-3-one-6-carboxylate**

This was prepared from methyl 1-acetyl-3-formylindole-6-carboxylate (1.03g, 4.20 mmol) using the method of Merour et al. (*Synthesis*, 1994, 411) to yield the formate (680 mg).

5 The formate was dissolved in THF (50ml) and treated with sat. NaHCO<sub>3</sub> solution (10ml). After 15 min. the reaction mixture was extracted with ethyl acetate, washed with water, dried and concentrated to give the ketone (574mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.3 (3H, br.), 3.9 (3H, s), 4.3 (2H, s), 7.75 (1H, d), 7.85 (1H, d), 9.1 (1H, br.); LCMS M+H 234.

10

**Methyl 1-acetyl-3-methoxyindole-6-carboxylate**

Methyl 1-acetyl-2,3-dihydroindol-3-one-6-carboxylate (233mg, 1 mmol), trimethyl orthoformate (10ml) and *p*-toluene sulphonic acid (20 mg) were heated under reflux for 3 h. in methanol (10ml). The reaction mixture was concentrated under reduced pressure, poured into water and extracted with chloroform. After drying and evaporation, the product was purified by prep hplc; <sup>1</sup>H NMR (CD<sub>3</sub>CN) 2.56 (3H, s), 3.93 (3H, s), 3.97 (3H, s), 7.25 (1H, s), 7.62 (1H, d), 7.90 (1H, d), 9.0 (1H, br.); LCMS M+H 248.

**3-Methoxyindole-6-carboxylic acid**

To a solution of methyl 1-acetyl-3-methoxyindole-6-carboxylate (74 mg, 0.3 mmol) in THF (10ml) and water (2ml) was added lithium hydroxide hydrate (63 mg, 1.5 mmol). The reaction mixture was warmed to 50°C and stirred for 3 h. The THF was removed under reduced pressure and the pH of the aqueous phase adjusted to 3. Extraction of the aqueous layer with ethyl acetate, drying and concentration gave the acid (50 mg, 87%); <sup>1</sup>H NMR (CD<sub>3</sub>CN) 3.75 (3H, s), 3.97 (3H, s), 6.9

(1H, s), 7.45 (1H, d), 7.55 (1H, d), 8.2 (1H, s); LCMS M+H  
192.

**1-(3-Methoxyindole-6-carbonyl-D-phenylglycanyl)-4,4'-(1'-  
5 methylbispiperidine)**

Prepared by coupling to D-phenylglycanyl-4,4'-(1'-methylbispiperidine) using EDC and HOAt as described previously.

Hplc (Luna C18, Gradient3) rt 8.35min.

10 LCMS M+1 489 Nmr.

**Example 156.**

**1-(3-Amino-4-chlorobenzoyl-D-cyclohexylglycanyl)-4-(4-fluoro-2-methylsulfonylphenyl)-piperazine**

15 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 15.37min.

LCMS M+1 551

**Example 157.**

**1-(3-Amino-4-chlorobenzoyl-D,L-1-naphthylglycanyl)-4-(4-fluoro-2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 15.69min.

LCMS M+1 595

25

**Example 158.**

**1-(3-Chloroindole-6-carbonyl-D,L-(2-methylthiazol-4-yl)glycanyl)-1`-methyl-4,4`-bispiperidine**

**Ethyl oximinoacetoacetate**

This was prepared from ethyl acetoacetate (10.00g) using the method of Fischer (*Organic Synthesis Coll. Vol. 3*, 513-516) to yield the titled compound (12.45g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.25 5 (3H, t), 2.35 (3H, s), 4.3 (2H, q), 8.8 (1H, br.).

**Ethyl- $\gamma$ -chloro- $\alpha$ -oximinoacetoacetate**

This was prepared from ethyl oximinoacetoacetate (1.73g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry, 1973, 16(9)*, 978-984) to yield the titled compound (1.44g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.25 (3H, t), 4.3 (2H, q), 4.55 (2H, s), 9.45 (1H, s), contains 20% starting material by NMR.

15   **Ethyl- $\alpha$ -oximino-2-methylthiazole-4-acetate**

This was prepared from ethyl- $\gamma$ -chloro- $\alpha$ -oximinoacetoacetate (1.44g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry, 1973, 16(9)*, 978-984) to yield the titled compound (0.64g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.35 (3H, t), 2.7 20 (3H, s), 4.35 (2H, q), 8.2 (1H, s).

**D,L-(2-methylthiazol-4-yl)glycine ethyl ester**

This was prepared from ethyl- $\alpha$ -oximino-2-methylthiazole-4-acetate (0.62g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry, 1973, 16(9)*, 978-984) to yield the titled compound (0.40g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.15 (3H, t), 1.95 25 (2H, br.), 2.6 (3H, s), 4.15 (2H, m), 4.65 (1H, s), 6.95 (1H, s).

**N-Boc-D,L-(2-methylthiazol-4-yl)glycine ethyl ester**

To a solution of D,L-(2-methylthiazol-4-yl)glycine ethyl ester (0.397g, 1.982 mmol) in tetrahydrofuran (20 cm<sup>3</sup>), was added di-*tert*-butyldicarbonate (0.475g, 2.180 mmol) and triethylamine (0.304 cm<sup>3</sup>, 2.180 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (c.a. 50 cm<sup>3</sup>) washed with 0.5% hydrochloric acid solution (c.a. 20 cm<sup>3</sup>), and saturated sodium bicarbonate solution (c.a. 20 cm<sup>3</sup>). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow oil (0.654g, 2.177 mmol) [~100% yield]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.1 (3H, s), 1.35 (9H, s), 2.6 (3H, s), 4.15 (3H, m), 5.3 (1H, d), 5.7 (1H, s), 7.0 (1H, s).

15

**N-Boc-D,L-(2-methylthiazol-4-yl)glycine**

To a solution of N-Boc-D,L-(2-methylthiazol-4-yl)glycine ethyl ester (0.595g, 1.982 mmol) in methanol (c.a. 15 cm<sup>3</sup>), was added 2M sodium hydroxide (1.98 cm<sup>3</sup>, 3.964 mmol), and allowed to stir for 30 minutes. The solution was concentrated *in vacuo* and taken up in water (c.a. 50 cm<sup>3</sup>). The aqueous solution was washed with ethyl acetate (c.a. 30 cm<sup>3</sup>), and then acidified to pH 2 with 5% hydrochloric acid solution (c.a. 50 cm<sup>3</sup>). The product was extracted with ethyl acetate (c.a. 3x60 cm<sup>3</sup>), dried over magnesium sulphate, and concentrated *in vacuo* to yield a pale yellow oil (0.645g, 2.368 mmol) [~100% yield]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.35 (9H, s), 2.6 (3H, s), 5.4 (1H, d), 5.9 (1H, s), 7.1 (1H, s).

30    **1-(N-Boc-D,L-(2-methylthiazol-4-yl)glyciny1) 1`-methyl-4,4`-**

**bis(piperidine**

Prepared by coupling N-Boc-D,L-(2-methylthiazol-4-yl)-glycine to 4,4`-(1`-methylbis(piperidine) di-HCl salt using EDC and HOAt as described previously;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.5-1.3 (10H, br.), 1.35 (9H, s), 1.4-1.85 (6H, br.), 2.2 (3H, d), 2.6 (3H, s), 3.75-4.0 (1H, br.), 4.55 (1H, br.), 5.7 (1H, d), 6.1 (1H, d), 6.95 (1H, d)

1-(D,L-(2-Methylthiazol-4-yl)glycanyl)-1`-methyl-4,4`-bis(piperidine

Prepared from 1-(N-Boc-D,L-(2-methylthiazol-4-yl)glycanyl)-1`-methyl-4,4`-bis(piperidine using DCM/TFA deprotection as described previously;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.9-1.8 (10H, br.), 2.1-2.3 (2H, br.), 2.45 (3H, br.), 2.6 (3H, s), 3.1-3.4 (3H, br.), 4.6 (1H, br.), 4.95 (1H, s), 6.85 (1H, d).

1-(3-Chloroindole-6-carbonyl-D,L-(2-Methylthiazol-4-yl)glycanyl)-1`-methyl-4,4`-bis(piperidine

Prepared by coupling 1-(D,L-(2-methylthiazol-4-yl)-glycanyl)-1`-methyl-4,4`-bis(piperidine to 3-chloroindole-6-carboxylic acid using EDC and HOAt as described previously;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.5-1.9 (12H, br.), 2.4 (2H, br.), 2.55 (3H, s), 2.65 (3H, s), 3.5 (2H, br.), 4.1 (1H, br.), 4.55 (1H, br.), 6.15 (1H, d), 7.15 (1H, d), 7.5 (2H, br.), 7.8-8.1 (2H, br.), 8.9-9.25 (1H, br.), 12.2-12.6 (1H, br. d); HPLC (Luna C18, Gradient3) rt 8.75min; LCMS M+1 514.

**Example 159.**

1-(3-Chloroindole-6-carbonyl-D,L-4-thiazolyglycanyl)-1`-

**methyl-4,4'-bis(piperidine****Ethyl- $\alpha$ -oximino-thiazole-4-acetate**

To a 2 necked r.b. flask (100 cm<sup>3</sup>) with ethanol thermometer, 5 concentrated sulphuric acid (25 cm<sup>3</sup>) was added and cooled to 0°C with stirring. To this solution, was added the ethyl- $\alpha$ -oximino-2-aminothiazole-4-acetate (5.00g, 23.231 mmol). Water (10 cm<sup>3</sup>) was then added and cooled to -10°C. A solution of sodium nitrite (1.683g, 24.393 mmol) in water (5 cm<sup>3</sup>) was then added slowly over an hour keeping the temperature below -5°C.

To a separate r.b. flask (500 cm<sup>3</sup>), water (180 cm<sup>3</sup>) was added and cooled to 3°C. The reaction solution was poured on to the cold water with stirring and then cooled to -5°C. To 15 this solution, 50% hypophosphoric acid (90 cm<sup>3</sup>) was added dropwise over 10 minutes keeping the temperature at -5°C. The solution was allowed to warm to room temperature and stirred overnight. The product was extracted with diethyl ether (c.a. 3x150 cm<sup>3</sup>) and washed with water. The ether 20 layer was concentrated *in vacuo* and treated to flash chromatography (50% ethyl acetate/n-hexane) to yield a orange oil upon concentration *in vacuo* (0.60g, 3.00 mmol) [13% yield]; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.35 (3H, m), 4.35 (2H, m), 8.4 (1H, s), 8.9 (1H, s), 14.4 (1H, s).

25

**D,L-4-thiazolylglycine ethyl ester**

This was prepared from ethyl- $\alpha$ -oximino-thiazole-4-acetate (0.60g) using the method of Hatanaka *et al.* (*Journal of Medicinal Chemistry*, 1973, 16(9), 978-984) to yield the

titled compound (0.46g);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.25 (3H, t), 1.8-2.3 (2H, br.), 4.1 (2H, m), 4.75 (1H, s), 7.25 (1H, d), 8.7 (1H, d).

5 **N-Boc-D,L-4-thiazolylglycine ethyl ester**

To a solution of D,L-4-thiazolylglycine ethyl ester (0.460g, 2.470 mmol) in tetrahydrofuran ( $20 \text{ cm}^3$ ), was added di-*tert*-butyldicarbonate (0.530g, 2.470 mmol) and triethylamine ( $0.344 \text{ cm}^3$ , 2.470 mmol). This was allowed to stir for 1 hour and the solution concentrated *in vacuo*. The oil was taken up in ethyl acetate (c.a.  $50 \text{ cm}^3$ ) washed with 0.5% hydrochloric acid solution (c.a.  $20 \text{ cm}^3$ ), and saturated sodium bicarbonate solution (c.a.  $20 \text{ cm}^3$ ). This was then dried over magnesium sulphate and concentrated *in vacuo* to yield an orange oil (0.709g, 2.477 mmol) [ $\sim 100\%$  yield];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.15 (3H, t), 1.35 (9H, s), 4.1 (2H, m), 5.45 (1H, d), 5.75 (1H, d), 7.3 (1H, d), 8.7 (1H, d).

**N-Boc-D,L-4-thiazolylglycine**

20 To a solution of N-Boc-D,L-4-thiazolylglycine ethyl ester (0.700g, 2.470 mmol) in methanol (c.a.  $15 \text{ cm}^3$ ), was added 2M sodium hydroxide ( $2.47 \text{ cm}^3$ , 4.940 mmol) and allowed to stir for 90 minutes. The solution was concentrated *in vacuo* and taken up in water (c.a.  $20 \text{ cm}^3$ ). The aqueous solution was washed with ethyl acetate (c.a.  $20 \text{ cm}^3$ ), and then acidified to pH 2 with 5% hydrochloric acid solution (c.a.  $50 \text{ cm}^3$ ). The product was extracted with ethyl acetate (c.a.  $3 \times 30 \text{ cm}^3$ ), dried over magnesium sulphate, and concentrated *in vacuo* to yield a pale yellow oil (0.582g, 2.254 mmol) [91% yield];  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.35 (9H, s), 5.5 (1H, d), 5.8 (1H,

d), 7.35 (1H, d), 8.75 (1H, d), 9.8-10.2 (1H, br.).

**1-(N-Boc-D,L-4-thiazolylglycanyl)-1`-methyl-4,4`-bis(piperidine)**

5 Prepared by coupling N-Boc-D,L-4-thiazolylglycine to 4,4`-(1`-methylbis(piperidine)) di-HCl salt using EDC and HOAt as described previously;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.8-1.25 (10H, br.), 1.35 (9H, m), 1.7 (6H, br.), 2.0 (6H, m), 2.4 (3H, br.), 3.1 (2H, br.), 3.7 (1H, d), 4.6 (1H, d), 5.8 (1H, d),  
10 6.0 (1H, br.), 7.25 (1H, 1H, br.), 8.65 (1H, m).

**1-(D,L-4-Thiazolylglycanyl)-1`-methyl-4,4`-bis(piperidine)**

Prepared from 1-(N-Boc-D,L-4-thiazolylglycanyl)-1`-methyl-4,4`-bis(piperidine) using DCM/TFA deprotection as described  
15 previously. The product was purified by prep HPLC; LCMS M+1 323.

**1-(3-Chloroindole-6-carbonyl-D,L-thiazol-4-ylglycanyl)-1`-methyl-4,4`-bis(piperidine)**

20 Prepared by coupling 1-(D,L-4-Thiazolylglycanyl)-1`-methyl-4,4`-bis(piperidine) to 3-chloroindole-6-carboxylic acid using EDC and HOAt as described previously;  $^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ) 0.5-2.0 (10H, br.), 2.5 (2H, m), 2.8 (3H, br.), 3.1 (2H, m), 3.5 (2H, br.), 4.2 (1H, d), 4.6 (1H, d), 6.4 (1H, m), 7.5  
25 (1H, br.), 7.8 (2H, br.), 8.15 (2H, br.), 9.05 (1H, br.), 9.9 (1H, br.); HPLC (Luna C18, Gradient3) rt 6.69min; LCMS M+1 500.

Preparation of starting materials:

**Boc-R-4-(carboxymethyl)phenylglycine**

5   **R-4-Hydroxyphenylglycine methyl ester hydrochloride.**

To a dry 250ml three necked round bottom flask, equipped with a low temperature thermometer, a septum for nitrogen coverage and another for introduction of thionyl chloride by syringe, was added R-4-hydroxyphenylglycine (12.5g) and dry methanol (24ml). The mixture was stirred (magnetic stirrer) and cooled to an internal temperature of -20°C using cardice/acetone. Using a syringe, thionyl chloride was added dropwise to the cooled mixture over a period of 10min. (Care: the reaction of thionyl chloride with methanol is very exothermic and rate of addition should be such that the thionyl chloride is efficiently stirred into the mixture and that the temperature does not rise above -20°C. Once the addition was complete the mixture was allowed to warm to room temperature overnight (16-18hr). Dry ether (150ml) was added and the white ppt. that formed was filtered off, washed with a little more ether and dried. Yield 15.5g 95%. Nmr.

**Boc-R-4-Hydroxyphenylglycine methyl ester hydrochloride**

25   To a stirred mixture of R-4-hydroxyphenylglycine methyl ester hydrochloride 14g and sodium bicarbonate 11.7g in tetrahydrofuran (THF) 150ml and water 50ml, was added in one portion, di- t-butyl dicarbonate 15.9g. The mixture was stirred rapidly to allow thorough mixing for 4h. Hexane (75ml) was added and the organic layer separated and washed

with sat. sodium bicarbonate solution, then brine and then dried with magnesium sulphate. The drying agents was filtered off and washed with a little THF and evaporated to dryness, finishing with a high vacuum pump to remove the last traces of di- t-butyl dicarbonate. Yield 19.7g 96%.

Nmr.

**Boc-R-4-(trifluoromethanesulphonyloxy)phenylglycine methyl ester hydrochloride**

To a stirred solution of Boc-R-4-hydroxyphenylglycine methyl ester 19g in dichloromethane 400ml was added 2,6-lutidine 9.44ml and 4-dimethylaminopyridine 1.65g and the mixture cooled in an ice bath. Trifluoromethanane-sulphonic anhydride 13.74ml was added over a period of 5min and then the reaction left to warm to room temperature over 4h. The organic solution was washed with water, 2 x 150ml, 1N HCl 2 x 150ml and the saturated sodium bicarbonate 150ml. The organics were dried with magnesium sulphate and then evaporated to an oil. The mixture was purified using flash chromatography ( $\text{SiO}_2$  250g eluting with 1:1 hexane/dichloromethane and then neat dichloromethane). Pure product fractions were combined and evaporated, finishing with a high vacuum pump to remove all traces of solvent, to give a white solid, 19g 77%. Nmr.

25

**Boc-R-4-(carboxymethyl)phenylglycine methyl ester.**

Boc-R-4-trifluoromethanesulphonyloxyphenylglycine methyl ester (15g), methanol (32.6ml), bis-1,3-diphenylphosphinylpropane (448mg), palladium (II) acetate (255mg), triethylamine (10.2ml) and dimethylformamide (72ml)

were placed in the glass liner of the Parr reactor and the reactor assembled. The vessel was pressurised to ~10psi with nitrogen and the gas released (repeated five times to remove all oxygen from the system). Carbon monoxide gas was then  
5 carefully introduced (use extreme care -the gas cylinder is pressurised to far beyond the bursting disc pressure of the Parr, ideally use a pressure regulator to reduce the pressure to ~100psi) to ~20psi and released three times (into the back of a fume hood). Carbon monoxide was then  
10 added to ~100psi and the stirrer started. The vessel was slowly heated to 65°C internal temperature and then stirred at 65°C overnight. (At the early stages more carbon monoxide was added to maintain ~100psi) A sample was removed after 18h and examined by tlc. When complete, the reaction was  
15 cooled to ~30°C, the gas released and the vessel flushed five times with nitrogen as before. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with 1M hydrochloric acid and then saturated sodium bicarbonate. The solution was dried with MgSO<sub>4</sub> and  
20 evaporated. Flash chromatography of the resulting oil gave the product, pure by tlc, 10.6g 90%. Nmr

**Boc-R-4-(carboxymethyl)phenylglycine.**

To a solution of Boc-R-4-carboxymethylphenylglycine methyl ester 692mg in THF 10ml was added a solution of lithium hydroxide hydrate 90mg in water 7ml. The mixture immediately became cloudy and over 15min cleared. After 30min, tlc showed the reaction to be complete. Ethyl acetate 20ml and water 20ml were added and the aqueous layer separated. The  
25 aqueous solution was acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 x 20ml). The organic

solution was then washed with water x 2 and brine x 2, dried with MgSO<sub>4</sub> and evaporated to give the mono-ester (650mg, 98%), pure by tlc. Nmr.

5   **Boc-R-4-(carboxybenzyl)phenylglycine methyl ester**

By the same method as described above, using 27.6g of Boc-R-4-trifluoromethanesulphonyloxyphenylglycine methyl ester and benzyl alcohol to give the Boc-D-4-(carboxybenzyl)phenylglycine methyl ester 18.7g pure, 70% plus a further 6g of impure material (the major contaminant is benzyl alcohol). Nmr

**Boc-R-4-(carboxamido)phenylglycine methyl ester**

15   **Boc-R-4-(carboxy)phenylglycine methyl ester**

Boc-R-4-(carboxybenzyl)phenylglycine methyl ester (500mg) was dissolved in THF containing Pd/C 10% (100mg) and hydrogenated at 1atm for 2h. Removal of the catalyst by filtration and evaporation of solvent gave Boc-R-4-(carboxy)phenylglycine methyl ester (330mg, 87%). Nmr.

**Boc-R-4-(carboxamido)phenylglycine methyl ester**

To a solution of Boc-R-4-(carboxy)phenylglycine methyl ester (3.5g) in DMF 30ml was added EDCI (2.60g 1.36mmol) and HOBT (1.4g 10.4mmol) and the mixture stirred for 10min before cooling in a ice bath and bubbling in ammonia gas for 5min. The mixture was stirred for 2h at room temperature and then diluted with ethyl acetate and washed with water. The

aqueous solution was extracted with a little ethyl acetate and the combined organics washed with brine. The organic solution was evaporated to an oil which was purified by flash chromatography ( $\text{SiO}_2$  - dichloromethane/ ethyl acetate 5 0 - 25%) to give Boc-R-4-(carboxamido)phenylglycine methyl ester (1.7g 48%). Nmr.

**Boc-R-4-(methylcarboxamido)phenylglycine methyl ester**

Was prepared by a similar method to that described above.

10 Nmr

**Boc-R-4-Methoxyphenylglycine.**

Boc-R-4-hydroxyphenylglycine methyl ester was converted to Boc-R-4-methoxyphenylglycine using the alkylation method 15 described by Basak et al. (Tetrahedron Lett. 1998, 39 (27), 4883-4886) followed by hydrolysis of the methyl ester with lithium hydroxide in aqueous THF. Nmr

**Boc-D,L-2-chlorophenylglycine**

20 2-Chlorobenzaldehyde (20mmol., 2.252ml) and 2,4 dimethoxybenzylamine (20mmol., 3.004ml) were added together and stirred for 2 hours. DCM (5ml) was added and any water separated and removed. tert-Butyl isonitrile (20mmol., 2.262ml) was added and stirred for 10mins followed by acetic acid (20mmol., 1.145ml). Stirring was continued for 3 days. The reaction mixture was then treated with TFA (30ml) and triethylsilane (5ml). After 3 hours the mixture was evaporated to dryness, 6M HCl (100ml) added and the whole refluxed overnight at 130°C, stirring rapidly. The mixture

was allowed to cool and extracted with EtOAc (50ml x2) the aqueous fraction was evaporated to dryness and treated with 2M NaOH solution. The mixture was extracted with EtOAc (50ml x2) excess boc anhydride (5.2g) in dioxan (20ml) was added 5 to the aqueous fraction and stirred overnight. The mixture was extracted with diethyl ether (100ml x2) acidified to pH 1 (cHCl) and extracted with EtOAc (50ml x2). The combined organic fractions were washed with water and evaporated to dryness under high vacuo The product Boc -2-chloro 10 phenylglycine (4.252g, 74.5%)

<sup>1</sup>H nmr (CD<sub>3</sub>CN/D<sub>2</sub>O) 7.3 (4H, m); 5.5 (1H, s); 1.3 (9H, s). MS 286 (M+1)

By a similar method the following amino acids were obtained

15

**Boc-D,L-3-fluorophenylglycine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN/D<sub>2</sub>O) 7.3 (1H, m), 7.1(3H, m); 5.2 (1H, s); 1.3 (9H, s). MS 270 (M+1)

20 **Boc-D,L-4-fluorophenylglycine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN/D<sub>2</sub>O) 7.3 (2H, m); 6.9 (2H, m), 5.0 (1H, s); 1.3 (9H, s). MS 270 (M+1)

**Boc-D,L-2-methylphenylglycine**

25 <sup>1</sup>H nmr (CD<sub>3</sub>CN/D<sub>2</sub>O) 7.3 (4H, m); 5.5 (1H, s); 2.5 (3H, s); 1.3 (9H, s). MS 266 (M+1)

**Boc-D,L-3-thienylglycine**

<sup>1</sup>H nmr (CD<sub>3</sub>CN/D<sub>2</sub>O) 7.5 (2H, m); 7.1 (1H, d); 5.3 (1H, s); 1.3 (9H, s). MS 258 (M+1)

5   **Boc-D,L-2-fluorophenylglycine**

Was obtained by treating D,L-2-fluorophenylglycine (Aldrich) with Boc anhydride (1.1eq) and 2M NaOH (1eq) in Ethanol. Aqueous work up as described above yielded the protected amino acid.

10   Nmr.

These protected aminoacids were then coupled with first an amine and then, after removal of the Boc protecting group, with a carboxylic acid by method 2 to give the following 15 inhibitor examples:

**Example 160.**

**1-(4-Methoxybenzoyl-D,L-3-thienylglyciny1)-4-(2-methylsulfonylphenyl)-piperazine**

20   Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.18  
LCMS M+1 514. Nmr.

**Example 161.**

**1-(Indol-6-carbonyl-D,L-3-thienylglyciny1)-4-(2-methylsulfonylphenyl)-piperazine**

25   Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.44  
LCMS M+1 523. Nmr.

**Example 162.**

**1-(4-Methoxybenzoyl-D,L-3-fluorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

5 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.61  
LCMS M+1 526. Nmr.

**Example 163.**

**1-(Indol-6-carbonyl-D,L-3-fluorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

10 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.88  
LCMS M+1 535. Nmr.

**Example 164.**

15 **1-(4-Methoxybenzoyl-D,L-4-fluorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.52  
LCMS M+1 526. Nmr.

20 **Example 165.**

**1-(Indol-6-carbonyl-D,L-4-fluorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.92  
LCMS M+1 535. Nmr.

**Example 166.**

**1-(4-Methoxybenzoyl-D,L-2-chlorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.82

5 LCMS M+1 542 Nmr.

**Example 167.**

**1-(Indol-6-carbonyl-D,L-2-chlorophenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

10 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.63

LCMS M+1 551 Nmr.

**Example 168.**

**1-(4-Methoxybenzoyl-D,L-2-methylphenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.69

LCMS M+1 522 Nmr.

**Example 169.**

20 **1-(Indol-6-carbonyl-D,L-2-methylphenylglyciny1) 4-(2-methylsulfonylphenyl)-piperazine**

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA) rt 10.76

LCMS M+1 531 Nmr.

**Example 170.**

**1-(Indol-6-carbonyl-D-2-fluorophenylglyciny1) 4-(4-fluoro -  
2-methylsulfonylphenyl)-piperazine**

Hplc (Luna 2 C18 3u water/acetonitrile/TFA, gradient = 5-  
5 100%MeCN over 7 min) rt 10.92

LCMS M+1 553 Nmr.

**Example 171.**

**1-(Indol-6-carbonyl-D- (4-carboxyphenylglyciny1) - (4-(1-  
10 methylpiperidin-4-yl)piperazine)**

By coupling of Boc-D-4-carboxymethylphenylglycine with 1-(4-(1-methylpiperidin-4-yl)piperazine) using HOAt and EDCI, followed by deprotection (TFA), coupling to indol-6-carboxylic acid using HOAt and EDCI followed by hydrolysis 15 of the methyl ester with lithium hydroxide.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
6.05min

LCMS M+1 504

Nmr.

20

**Example 172.**

**1-(Indol-6-carbonyl-D-phenylglyciny1)-4-(4-  
hydroxyphenyl)piperazine**

By coupling of Boc-D-phenylglycine with 1-(4-hydroxyphenyl)piperazine using HOAt and EDCI, followed by deprotection (TFA) and coupling to indol-6-carboxylic acid using HOAt and EDCI.

Hplc (Symmetry C8, Gradient3, water/acetonitrile/TFA), rt,

6.0min

LCMS M+1 455

Nmr.

5 **Example 173.**

**1-(3-Chloroindol-6-carbonyl-D-phenylglycyl)-4-(4-hydroxyphenyl)piperazine**

By coupling of Boc-D-phenylglycine with 1-(4-hydroxyphenyl)piperazine using HOAt and EDCI, followed by 10 deprotection (TFA) and coupling to 3-chloroindol-6-carboxylic acid using HOAt and EDCI.

Hplc (Symmetry C8, Gradient3, water/acetonitrile/TFA), rt, 6.55min

LCMS M+1 489

15 Nmr.

**Example 174.**

**1-(4-methoxybenzoyl-D-4-methoxyphenylglycyl)-4-(2-methylsulphonylphenyl)piperazine**

20 By coupling of Boc-D-4-methoxyphenylglycine with-(2-methylsulphonylphenyl)piperazine using HOAt and EDCI, followed by deprotection (TFA) and coupling to 4-methoxybenzoic acid using HOAt and EDCI.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 25 10.4min

LCMS M+1 538

Nmr.

**Example 175.**

**1-(5-Fluoroindole-6-carbonyl-D-phenylglycinyl)-1-methyl-4,4'-bis(piperidine).**

5

**N-(2,2-Dimethoxyethyl)-4-fluoro-3-methoxyaniline**

To a solution of 4-fluoro-3-methoxyaniline (0.98g 6.9mmol) in ethanol (20ml) was added glyoxal 1,1-dimethyl acetal (0.89g 8.27mmol). Pd/C 5% (50mg) was added and the mixture 10 hydrogenated. Removal of the catalyst by filtration and evaporation of solvent *in vacuo* gave N-(2,2-dimethoxyethyl)-4-fluoro-3-methoxyaniline 1.6g

NMR LCMS M+1 (less MeO) 199

15 **N-(2,2-Dimethoxyethyl)-N-methanesulphonyl-4-fluoro-3-methoxyaniline**

N-(2,2-dimethoxyethyl)-4-fluoro-3-methoxyaniline (1.46g, 6.37mmol) in dichloromethane (20ml) was treated with pyridine (0.5g 6.37mmol) and methanesulphonyl chloride 20 (766mg, 6.69mmol) and the mixture stirred until the reaction was complete by tlc. Aqueous work up and removal of solvent *in vacuo* gave N-(2,2-dimethoxyethyl)-N-methanesulphonyl-4-fluoro-3-methoxyaniline 1.91g

NMR

25

**5-Fluoro-1-methanesulphonyl-6-methoxyindole**

To a solution of N-(2,2-dimethoxyethyl)-N-methanesulphonyl-4-fluoro-3-methoxyaniline (1.91g, 0.65mmol) in dry toluene

at 0°C under argon, was added slowly a solution of TiCl<sub>4</sub> (0.173g, 0.911mmol) in dry toluene (10ml). The solution was then heated to 70°C for 1h. cooled and poured onto ice/sat. sod. bicarbonate solution (20ml). The organic layer was separated, washed with sat. sod. bicarbonate solution, 0.5% hydrochloric acid (2 x 20ml) and water (2 x 20ml). The solution was dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give 5-fluoro-1-methanesulphonyl-6-methoxyindole ((0.102g)

NMR

10

**5-Fluoro-6-hydroxy-1-methanesulphonylindole**

To a solution of 5-fluoro-1-methanesulphonyl-6-methoxyindole (0.10g 0.41mmol) in dry dichloromethane (3ml) at -10°C was added a solution of BBr<sub>3</sub> (1M in dichloromethane, 1.23ml) over one minute. The reacture was warmed to room temperature and stirred for 2h and then poured onto ice/1M hydrochloric acid (10ml). After stirring for 15min the mixture was extracted with ethyl acetate (1 x 50ml, 2x 20ml), dried (MgSO<sub>4</sub>) and evaporated *in vacuo* to give 5-fluoro-6-hydroxy-1-methanesulphonylindole (70mg)

NMR

**5-Fluoro-1-methanesulphonyl-6-trifluoromethanesulphonyloxy-indole**

25 To a solution of 5-fluoro-6-hydroxy-1-methanesulphonylindole (0.57mg, 2.49mmol) in dry dichloromethane (20ml) at 0°C was added pyridine (0.24ml, 2.99mmol) and then trifluoromethanesulphonic anhydride (0.50ml, 2.99mmol) and the mixture stirred for 2h. The reaction mixture was washed 30 with 0.5% hydrochloric acid (2 x 50ml), sodium bicarbonate

solution (2 x 50ml) and water (50ml), dried ( $MgSO_4$ ) and filtered through a short pad of silica. Evaporation of solvent *in vacuo* gave 5-fluoro-1-methanesulphonyl-6-trifluoromethanesulphonyloxy-indole, (0.67g).

5 NMR

**Methyl 5-fluoro-1-methanesulphonyl-indol-6-carboxylate,**

To a solution of 5-fluoro-1-methanesulphonyl-6-trifluoromethanesulphonyloxy-indole, (0.70g 1.94mmol) was added, Pd (II) acetate (14mg), bis 1,3-diphenylphosphinylpropane (24mg), dimethylformamide (4ml) and methanol (2ml) and triethylamine (0.54ml) and the mixture stirred for 2 min. Carbon monoxide gas was bubbled in for 15min and then the mixture was heated to 75°C under an atmosphere of carbon monoxide and stirred overnight.

After cooling to room temperature the mixture was poured into ethyl acetate (80ml) and washed with 1M hydrochloric acid (50ml), sat. sod. bicarbonate (50ml) and water (50ml).

Drying ( $MgSO_4$ ), evaporation of solvent gave crude product (0.53g). Purification of a portion (225mg) by flash chromatography ( $SiO_2$ , 25% ethyl acetate in hexane) gave methyl 5-fluoro-1-methanesulphonyl-indol-6-carboxylate, (173mg)

NMR

25

**5-fluoro-1-methanesulphonyl-indol-6-carboxylic acid**

To a solution of methyl 5-fluoro-1-methanesulphonyl-indol-6-carboxylate (173mg) in THF (15ml) and water (2ml) was added 2M lithium hydroxide solution (3 equiv) and the mixture heated to 50°C for 2h. and then allowed to cool overnight.

The solution was concentrated *in vacuo*, diluted with 2M sodium hydroxide solution (10ml) and washed with ethyl acetate. The aqueous solution was acidified to pH3 with conc. hydrochloric acid and extracted with ethyl acetate (3 x 30ml). The organic solution was evaporated *in vacuo* to give 5-fluoro-1-methanesulphonyl-indol-6-carboxylic acid (164mg) - (circa 80% pure)

NMR

10 **1-(5-fluoro-1-methanesulphonyl-indol-6-carbonyl-D-phenylglycinyl-4,4'-(1'-methylbispiperidine))**

5-fluoro-1-methanesulphonyl-indol-6-carboxylic acid (164mg) was coupled to D-phenylglycinyl-4,4'-(1'-methylbispiperidine) using EDCI/HOAt as previously described 15 to give 1-(5-fluoro-1-methanesulphonyl-indol-6-carbonyl-D-phenylglycinyl-4,4'-(1'-methylbispiperidine)) (111mg) - (~70% pure)

NMR

20 **1-(5-fluoroindol-6-carbonyl-D-phenylglycinyl-4,4'-(1'-methylbispiperidine))**

1-(5-fluoro-1-methanesulphonyl-indol-6-carbonyl-D-phenylglycinyl-4,4'-(1'-methylbispiperidine)) (111mg--70% pure) was refluxed in ethanol (5ml) and sodium hydroxide 25 solution (34mg in 0.34ml) for 2.25h. The mixture was evaporated to dryness, taken up in water (10ml) and extracted with chloroform (60ml). The organic solution was dried ( $MgSO_4$ ) and evaporated *in vacuo* and the residue purified by Prep Hplc. To give 1-(5-fluoroindol-6-carbonyl-D-phenylglycinyl-4,4'-(1'-methylbispiperidine)) (19mg)

Hplc (Luna C18 Gradient 3) rt 11.37min

LCMS M+1 477

NMR

5   **Example 176.**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-pyridoxy)piperidinamide**

**1-t-Butoxycarbonyl-4-(2-pyridoxy)piperidine**

10   1-t-Butoxycarbonyl-4-piperidinol (5.0g 24.88mmol) in dry dimethylformamide (60ml) was treated with sodium hydride (60% 2.99g 74.75mmol) at room temperature under argon and then with 2-chloropyridine hydrochloride (4.1g 27.33mmol). Then mixture was heated at 80°C overnight. After cooling the  
15   reaction was carefully quenched with water (5ml) and then diluted with more water (20ml) and extracted with ethyl acetate (30ml). The organic solution was washed with sat. sodium bicarbonate, dried ( $MgSO_4$ ) and evaporated to give 1-t-butoxycarbonyl-4-(2-pyridoxy)piperidine (4.96g 72%)

20

**4-(2-pyridoxy)piperidine dihydrochloride.**

1-t-Butoxycarbonyl-4-(2-pyridoxy)piperidine (6.5g) was treated with a solution of hydrogen chloride in ethyl acetate (110ml) for 7h and the mixture evaporated to give 4-(2-pyridoxy)piperidine dihydrochloride, (7.4g 90%)  
25

**1-(Benzoyloxycarbonyl-D-phenylglycinyl)-4-(2-pyridoxy)piperidinamide**

Benzylloxycarbonyl-D-phenylglycine (3.75g 13.14mmol) was coupled to 4-(2-pyridoxy)piperidine dihydrochloride (3.0g 11.94mmol) using EDCI (2.52g 13.14g), HOAt (1.79g 13.13mmol) and triethylamine (3.63g 35.87mmol) to give, after work up with ethyl acetate and sodium bicarbonate solution, 1-(benzyloxycarbonyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide, (4.9g 92%)

**1-D-phenylglycanyl-4-(2-pyridoxy)piperidinamide**

10 1-(Benzyloxycarbonyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide (400mg) was hydrogenated in ethanol with 5% Pd/C overnight. Removal of catalyst and evaporation of solvent gave 1-D-phenylglycanyl-4-(2-pyridoxy)piperidinamide (162mg 58%)

15

Using a similar method and the appropriate starting materials the following intermediates were also prepared:

**1-(D-phenylglycanyl)-4-(4-pyridoxy)piperidinamide**

20 **1-(D-phenylglycanyl)-3-R,S-(4-pyridoxy)pyrrolidinamide**  
**1-(D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide**

25 1-D-phenylglycanyl-4-(2-pyridoxy)piperidinamide (162mg 0.52mmol) was treated with triethylamine (58mg 0.573mmol) and p-anisoyl chloride (93mg 0.545mmol) in dry dichloromethane for 1h. The reaction mixture was washed with sodium bicarbonate solution and brine, dried ( $MgSO_4$ )

and evaporated to an oil. Flash chromatography gave the product 1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide, (60mg 26%)

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,

5 8.94min

LCMS M+Na 468

Nmr

By a similar method the following compounds were prepared:

10

**Example 177.**

**1-(Indol-6-carbonyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide**

By the coupling of indol-6-carboxylic acid and 1-D-

15 phenylglycanyl-4-(2-pyridoxy)piperidinamide using EDCI and HOAt.

LCMS M+1 455

Nmr

20 **Example 178.**

**1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-4-(2-pyridoxy)piperidinamide**

By the coupling of 3-chloroindol-6-carboxylic acid and 1-D-

phenylglycanyl-4-(2-pyridoxy)piperidinamide using EDCI and

25 HOAt.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,

10.29min

LCMS M+1 489

Nmr

**Example 179.**

5   **1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-4-(4-pyridoxy)piperidinamide**

By the coupling of 3-chloroindol-6-carboxylic acid and 1-D-phenylglycanyl-4-(4-pyridoxy)piperidinamide using EDCI and HOAt.

10   Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
      8.16min

LCMS M+1 489

Nmr

15   **Example 180.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-pyridoxy)piperidinamide**

By the coupling of p-anisoyl chloride and 1-D-phenyl-glycanyl-4-(4-pyridoxy)piperidinamide in dichloromethane  
20   with triethylamine

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
      7.0min

LCMS M+1 446

Nmr

25

**Example 181.**

**1-(Indol-6-carbonyl-D-phenylglycanyl)-4-(4-**

**pyridoxy)piperidinamide**

By the coupling of indol-6-carboxylic acid and 1-D-phenylglycinyl-4-(4-pyridoxy)piperidinamide with EDCI and HOAt.

5 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
7.08min

LCMS M+1 455

Nmr

10 **Example 182.**

**1-(4-Methoxybenzoyl-D-phenylglycinyl)-3-R,S-(4-pyridoxy)pyrrolidinamide**

By the coupling of p-anisoyl chloride and 1-(D-phenylglycinyl)-3-R,S-(4-pyridoxy)pyrrolidinamide in dichloromethane with triethylamine

15 LCMS M+1 432

Nmr

**Example 183.**

20 **1-(Indol-6-carbonyl-D-phenylglycinyl)-3-R,S-(4-pyridoxy)pyrrolidinamide**

By the coupling indol-6-carboxylic acid and 1-(D-phenylglycinyl)-3-R,S-(4-pyridoxy)pyrrolidinamide with EDCI and HOAt

25 LCMS M+1 441

Nmr

**Example 184.**

**1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-3-R,S-(4-pyridoxy)pyrrolidinamide**

By the coupling 3-chloroindol-6-carboxylic acid and 1-(D-phenylglycanyl)-3-R,S-(4-pyridoxy)pyrrolidinamide with EDCI and HOAt

LCMS M+1 475

Nmr

10 **Example 185.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide**

By the coupling of p-anisoyl chloride and 1-(D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide in dichloromethane with triethylamine

LCMS M+1 432

Nmr

**Example 186.**

20 **1-(3-Chloroindol-6-carbonyl-D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide**

By the coupling 3-chloroindol-6-carboxylic acid and 1-(D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide with EDCI and HOAt

,  
25 LCMS M+1 475

Nmr

**Example 187.**

**1-(Indol-6-carbonyl-D-phenylglycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide**

By the coupling indol-6-carboxylic acid and 1-(D-phenyl-glycanyl)-3-R,S-(2-pyridoxy)pyrrolidinamide with EDCI and HOAt

LCMS M+1 441

Nmr

10 **Example 188.**

**1-(4-methoxybenzoyl-D-4-hydroxyphenylglycanyl)-4-(2-methylsulphonylphenyl)piperazine**

By coupling of Boc-D-4-hydroxyphenylglycine with-(2-methylsulphonylphenyl)piperazine using HOAt and EDCI, followed by deprotection (TFA) and coupling to 4-methoxybenzoic acid using HOAt and EDCI.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt, 9.1min

LCMS M+1 524

20 Nmr.

**Example 189.**

**1-(Indol-6-carbonyl-D-4-hydroxyphenylglycanyl)-4-(2-methylsulphonylphenyl)piperazine**

25 By coupling of Boc-D-4-hydroxyphenylglycine with-(2-methylsulphonylphenyl)piperazine using HOAt and EDCI, followed by deprotection (TFA) and coupling to 6-indole carboxylic acid using HOAt and EDCI.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
9.0min

LCMS M+1 533

Nmr.

5

**Example 190.**

**1-(Indol-6-carbonyl-D-4-hydroxyphenylglycinyl)-1`-methyl-4,4`-bispiperidine**

By coupling of Boc-D-4-hydroxyphenylglycine with 4,4`-(1`-  
10 methylbispiperidine) di-HCl salt using HOAt and EDCI,  
followed by deprotection (TFA) and coupling to 6-indole  
carboxylic acid using HOAt and EDCI.

Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
6.8min

15 LCMS M+1 475

Nmr.

**Example 191.**

**1-(3-Chloroindol-6-carbonyl-D-4-hydroxyphenylglycinyl)-1`-methyl-4,4`-bispiperidine**

By coupling of Boc-D-4-hydroxyphenylglycine with 4,4`-(1`-  
methylbispiperidine) di-HCl salt using HOAt and EDCI,  
followed by deprotection (TFA) and coupling to 3-  
chloroindole-6-carboxylic acid using HOAt and EDCI.

25 Hplc (Luna C18, Gradient3, water/acetonitrile/TFA), rt,  
7.3min

LCMS M+1 509

Nmr.

In the following examples the following additional abbreviations and meanings are included: CI-MS, chemical ionization mass spectrum; DMSO, dimethyl sulfoxide (perdeuterated if for NMR); EtOAc, ethyl acetate; EtOH, ethanol; IS-MS, ion spray mass spectrum; RP-HPLC, reverse phase HPLC; SCX, strong cation exchange resin; THF, tetrahydrofuran; TLC, thin layer chromatography with  $R_f$  as relative mobility;

Reagents were obtained from a variety of commercial sources.

IR means an infrared spectrum was obtained.  $^1\text{NMR}$ ,  $^1\text{H-NMR}$ , or  $^1\text{H}$  NMR means a proton magnetic resonance spectrum was obtained.

In general in this specification, "D-" or "R-" in the name of a product indicates the product was made beginning with a chiral starting material, for example D-phenylglycine; however, racemization may have occurred, and the enantiomeric purity may not have been determined.

**Examples 201-210**

25   **Preparation of Starting Materials**

**4-[(Benzylloxycarbonyl-D-phenylglycinyl)aminomethyl]-1-Boc-piperidine**

Using Coupling Method C, benzylloxycarbonyl-D-phenylglycine (10.4 g, 36.5 mmol) and 4-aminomethyl-1-Boc-piperidine (7.3 g, 36.5 mmol) afforded, after purification by column

chromatography ( $\text{SiO}_2$ : 4:1 to 3:2 hexanes:EtOAc), 10.2 g (58%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 482 (M+1).

5

**4-[(D-Phenylglycinyl)aminomethyl]-1-Boc-piperidine**

**(Deprotection Method C)** A solution of 4-[(benzyloxycarbonyl-D-phenylglycinyl)aminomethyl]-1-Boc-piperidine (9.00 g, 18.7 mmol) and 10% palladium on carbon (2.34 g) in EtOAc (80 mL):EtOH (200 mL) was placed under an atmosphere of hydrogen gas (balloon). After 16 h, the mixture was filtered and concentrated affording 6.31 g (98%) of the title compound, which was used without further purification.

$^1\text{NMR}$

15 IS-MS, m/e 348 (M+1).

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-Boc-piperidine**

**(Acylation Method C)** A solution of 4-[(D-phenylglycinyl)-aminomethyl]-1-Boc-piperidine (2.38 g, 6.88 mmol) and pyridine (8 mL) in methylene chloride was treated with 4-methoxybenzoyl chloride (1.76 g, 10.3 mmol) in methylene chloride (prepared by treatment of 4-methoxy benzoic acid with excess oxalyl chloride in methylene chloride followed by concentration). After 2 days, the mixture was partitioned between water and methylene chloride. The organic extracts were washed with 1 N HCl, water, 1 N NaOH and brine, and concentrated. The residue was purified by column chromatography ( $\text{SiO}_2$ : 1:1 to 1:3 hexanes:EtOAc), affording 2.33 g (71%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 482 (M+1)

Analysis for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>5</sub>:

Calcd: C, 67.3; H, 7.3; N, 8.7;

Found: C, 67.4; H, 7.4; N, 8.7.

5 **4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-piperidine**

Using Deprotection Method D, 4-[(4-methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-Boc-piperidine (2.38 g) afforded 1.56 g (82%) of 4-[(4-methoxybenzoyl-D-phenyl-

10 glycinyl)aminomethyl]piperidine.

<sup>1</sup>NMR

IS-MS, m/e 382 (M+1)

15 **General Procedure:** Unless otherwise indicated, the product of Examples 201-210 was prepared from 4-[(4-methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine and the indicated aldehyde or ketone using Alkylation Method D.

**Example 201.**

20 **4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-isopropylpiperidine**

4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine (0.10 g, 0.26 mmol) and acetone afforded 89 mg (81%) of the title compound.

25 <sup>1</sup>NMR

IS-MS, m/e 424 (M+1)

Analysis for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>:

Calcd: C, 70.9; H, 7.9; N, 9.9;

Found: C, 70.8; H, 7.8; N, 9.9.

**Example 202.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-(3-pentyl)piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine

5 (0.10 g, 0.26 mmol) and 3-pantanone afforded 57 mg (49%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 452 (M+1)

10 **Example 203.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-(2-indanyl)piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine

(0.10 g, 0.26 mmol) and 2-indanone afforded 91 mg (78%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 498 (M+1)

Analysis for  $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$ :

Calcd: C, 74.8; H, 7.1; N, 8.4;

20 Found: C, 74.5; H, 7.0; N, 7.9.

**Example 204.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-cyclopentylpiperidine**

25 4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine

(0.10 g, 0.26 mmol) and cyclopantanone afforded 101 mg (86%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 450 (M+1)

**Example 205.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-(cyclohexylmethyl)piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine

5 (0.10 g, 0.26 mmol) and cyclohexanecarboxaldehyde afforded 98 mg (79%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 478 (M+1)

10 **Example 206.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-cyclohexylpiperidine**

4-[(4-methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine (0.10 g, 0.26 mmol) and cyclohexanone afforded 95 mg (79%)

15 of the title compound.

$^1\text{NMR}$

IS-MS, m/e 464 (M+1)

20 **Example 207.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-(tetrahydropyran-4-yl)piperidine**

4-[(4-methoxybenzoyl-D-phenylglycinyl)aminomethyl]piperidine (0.10 g, 0.26 mmol) and tetrahydro-4H-pyran-4-one afforded 78 mg (65%) of the title compound.

25  $^1\text{NMR}$

IS-MS, m/e 466 (M+1)

20 **Example 208.**

**4-[(4-Methoxybenzoyl-D-phenylglycinyl)aminomethyl]-1-(tetrahydrothiopyran-4-yl)piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]piperidine (0.10 g, 0.26 mmol) and tetrahydro-4H-thiopyran-4-one afforded 63 mg (50%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 482 (M+1)

**Example 209.**

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]-1-methyl-piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]piperidine (60 mg, 0.16 mmol) and paraformaldehyde afforded 59 mg (93%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 396 (M+1)

15

**Example 210.**

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]-1-ethyl-piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]piperidine (60 mg, 0.16 mmol) and acetaldehyde afforded 23 mg (35%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 410 (M+1)

25 **Examples 211-213**

**Preparation of Starting Materials**

**4-[(Indole-6-carbonyl-D-phenylglycanyl)aminomethyl]-1-Boc-piperidine**

Using Coupling Method C, 4-[(D-phenylglycanyl)aminomethyl]-1-Boc-piperidine (2.5 g, 6.8 mmol) and indole-6-carboxylic acid (1.2 g, 7.6 mmol) afforded, after purification by

column chromatography ( $\text{SiO}_2$ : 2:3 hexanes:EtOAc to EtOAc), 2.57 g (83%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 491 (M+1)

5

**4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-piperidine**

Using Deprotection Method D, 4-[(indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-1-Boc piperidine (1.6 g, 3.3 mmol) afforded 4-[(indole-6-carbonyl-D-phenylglycinyl)aminomethyl]piperidine (1.27 g, 79%).

$^1\text{NMR}$

IS-MS, m/e 391 (M+1)

15 **General Procedure:** Unless otherwise indicated, the product of Examples 211-213 was prepared from 4-[(indole-6-carbonyl-D-phenylglycinyl)aminomethyl]piperidine and the indicated aldehyde or ketone using Alkylation Method D.

20 **Example 211.**

**4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-1-isopropylpiperidine**

4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-piperidine (0.10 g, 0.26 mmol) and acetone afforded 16 mg (14%) of the title compound.

$^1\text{NMR}$

IS-MS, m/e 433 (M+1)

**Example 212.**

**4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-1-cyclopentylpiperidine**

4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-piperidine (0.10 g, 0.26 mmol) and cyclohexanone afforded 19 mg (16%) of the title compound.

<sup>1</sup>NMR

5 IS-MS, m/e 459 (M+1)

**Example 213.**

**4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-1-cyclohexylmethylpiperidine**

10 4-[(Indole-6-carbonyl-D-phenylglycinyl)aminomethyl]-piperidine (0.10 g, 0.26 mmol) and cyclohexanecarboxaldehyde afforded 14 mg (11%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 487 (M+1)

15

**Examples 214-217**

**Preparation of Starting Materials**

**4-[(Benzylloxycarbonyl-D-phenylglycinyl)]-1-Boc-piperidine**

20 Using Coupling Method C, D-phenylglycine (6.10 g, 21.4 mmol) and 4-amino-1-Boc-piperidine (4.27 g, 21.4 mmol) afforded, after purification by column chromatography (SiO<sub>2</sub>: 7:3 hexanes:EtOAc), 8.44 g (84%) of the title compound.

<sup>1</sup>NMR

25 IS-MS, m/e 468 (M+1).

Analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>:

Calcd: C, 66.3; H, 7.1; N, 9.0;

Found: C, 66.5; H, 7.1; N, 9.0.

30 **4-[(D-Phenylglycinyl)amino]-1-Boc-piperidine**

Using Deprotection Method C, 4-[(benzylloxycarbonyl-D-phenylglycinyl)amino]-1-Boc-piperidine (8.0 g, 17 mmol)

afforded 6.1 g (90%) of the title compound, which was used without further purification.

<sup>1</sup>NMR

IS-MS, m/e 334 (M+1).

5

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]-1-Boc-piperidine**

Using Acylation Method C, 4-[(D-phenylglycanyl)amino]-1-Boc piperidine (2.23 g, 6.7 mmol) afforded, after purification by column chromatography (SiO<sub>2</sub>: 1:1 hexanes EtOAc), 2.44 g (78%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 468 (M+1).

15   **4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]piperidine**

Using Deprotection Method D, 4-[(4-methoxybenzoyl-D-phenylglycanyl)amino]-1-Boc-piperidine (2.32 g) afforded 1.53 g (84%) of 4-[(4-methoxybenzoyl-D-phenylglycanyl)-aminolpiperidine.

20   <sup>1</sup>NMR

IS-MS, m/e 368 (M+1).

**General Procedure:** Unless otherwise indicated, the product of Examples 214-217 was prepared from 4-[(4-methoxybenzoyl-D-phenylglycanyl)amino]piperidine and the indicated aldehyde or ketone using Alkylation Method D.

**Example 214.**

30   **4-[(4-Methoxybenzoyl-D-phenylglycanyl)aminomethyl]-1-(3-pentyl)piperidine**

4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]piperidine (0.11 g, 0.3 mmol) and 3-pentanone afforded 81 mg (62%) of the title compound.

<sup>1</sup>NMR

5 IS-MS, m/e 438 (M+1).

**Example 215.**

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]-1-(2-indanyl)-piperidine**

10 4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]piperidine (0.11 g, 0.3 mmol) and 2-indanone afforded 121 mg (83%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 484 (M+1).

15

**Example 216.**

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]-1-cyclopentyl-piperidine**

20 4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]piperidine (0.11 g, 0.3 mmol) and cyclopentanone afforded 103 mg (79%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 436 (M+1).

25 **Example 217.**

**4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]-1-cyclohexyl-piperidine**

30 4-[(4-Methoxybenzoyl-D-phenylglycanyl)amino]piperidine (0.11 g, 0.3 mmol) and 2-cyclohexanone afforded 112 mg (83%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 450 (M+1).

**Examples 218-220****Preparation of Starting Materials**

5   **4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]-1-Boc-piperidine**

Using Acylation Method C, 4-[(D-phenylglycinyl)amino]-1-Boc-piperidine (2.24 g, 6.15 mmol) and indole-6-carboxylic acid afforded 4-[(indole-6-carbonyl-D-phenylglycinyl)amino]-1-Boc-piperidine (2.66 g, 82%).

<sup>1</sup>NMR

IS-MS, m/e 477 (M+1).

**4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]piperidine**

15   Using Deprotection Method C, 4-[(indole-6-carbonyl-D-phenylglycinyl)amino]-1-Boc-piperidine (1.2 g, 2.5 mmol) afforded 4-[(indole-6-carbonyl-D-phenylglycinyl)amino]-piperidine (0.81 g, 83%).

<sup>1</sup>NMR

20   IS-MS, m/e 377 (M+1).

**General Procedure:** Unless otherwise indicated, the product of Examples 218-220 was prepared from 4-[(indole-6-carbonyl-D-phenylglycinyl)amino]piperidine and the indicated aldehyde or ketone using Alkylation Method D.

**Example 218.**

**4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]-1-isopropyl-piperidine**

30   4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]piperidine (0.10 g, 0.27 mmol) and acetone afforded 21 mg (19%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 419 (M+1).

**Example 219.**

5   **4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]-1-cyclopentylpiperidine**

4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]piperidine (0.10 g, 0.27 mmol) and cyclopentanone afforded 28 mg (24%) of the title compound.

10   <sup>1</sup>NMR

IS-MS, m/e 445 (M+1).

**Example 220.**

15   **4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]-1-(cyclohexylmethyl)piperidine**

4-[(Indole-6-carbonyl-D-phenylglycinyl)amino]piperidine (0.10 g, 0.27 mmol) and cyclohexanecarboxaldehyde afforded 17 mg (14%) of the title compound.

<sup>1</sup>NMR

20   IS-MS, m/e 473 (M+1).

**Examples 221-246**

**Preparation of Starting Materials**

25   **1-Methyl-4,4'-bispiperidine hydrobromide dihydribromide**

A solution of 4,4'-bipyridine (34.2 g, 100 mmol) in acetone was treated with methyl p-toluenesulfonate.

After 3 days, the salt (28 g, 80%) was isolated by filtration. The salt (44.0 g) was then treated with 10% Pd/C in acetic acid (400 mL) and hydrogen gas (4.1 bar) at 60 °C. After 16 h, the mixture was concentrated, the residue was dissolved in acetone, and then treated with

hydrogen bromide in acetic acid. The resulting salt (36 g, 86%) was isolated by filtration as a dihydروبromide.

<sup>1</sup>NMR

5   **5 - (D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

Using Coupling Method A, benzyloxycarbonyl-D-phenylglycine (16 g, 56 mmol) and 1-methyl-4,4'-bis(piperidine) dihydروبromide (17.2 g, 50 mmol) afforded, after treatment of the crude acylation product with HBr (150 mL) and acetic acid (150 mL) at 60 °C for 6 h, 8.4 g (54%) of the title compound.

<sup>1</sup>NMR

ES-MS, m/e 316 (M+1)

Analysis for C<sub>19</sub>H<sub>29</sub>N<sub>3</sub>O:

15   Calcd:   C, 72.3; H, 9.3; N, 13.3;  
      Found:   C, 71.9; H, 9.2; N, 13.1.

**General Procedure:** Unless otherwise indicated, the product of Examples 221-246 (or a protected derivative thereof) was prepared from 1-(D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) and the indicated acid using procedures similar to Acylation Method C.

**Removal of Protecting Group:** Where a protecting group was present in the acylation procedure, the procedure for its removal is described.

**Example 221.**

30   **1-(4-Methoxy-3-methylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.64 mmol) and 4-methoxy-3-methylbenzoic acid (116 mg, 0.70 mmol) afforded 159 mg (54%) of the title compound.

<sup>1</sup>NMR

5 IS-MS, m/e 464 (M+1)

Analysis for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>·0.35 H<sub>2</sub>O:

Calcd: C, 71.6; H, 8.1; N, 8.9;

Found: C, 71.5; H, 7.8; N, 9.0.

10 Example 222.

**1-[5-Methylthiophene-2-carbonyl-D-phenylglycinyl]-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.64 mmol) and 5-methylthiophene-2-carboxylic acid (120 mg, 0.70 mmol) afforded 190 mg (63%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 472 (M+1)

Example 223.

**20 1-(3-Chloro-4-methoxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.64 mmol) and 3-chloro-4-methoxybenzoic acid (130 mg, 0.70 mmol) afforded 182 mg (59%) of the title compound.

25 <sup>1</sup>NMR

IS-MS, m/e 484 (M+1)

Example 224.

**30 1-(5-Methoxybenzofuran-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.64 mmol) and 5-methoxybenzofuran-2-carboxylic acid (135 mg, 0.70 mmol) afforded 298 mg (96%) of the title compound.

<sup>1</sup>NMR

5 IS-MS, m/e 490 (M+1)

Analysis for C<sub>29</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>:

Calcd: C, 71.1; H, 7.2; N, 8.6;

Found: C, 71.5; H, 7.4; N, 8.8.

10 Example 225.

**1-(5-Acetylthiophene-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.64 mmol) and 5-acetylthiophene-2-carboxylic acid (119 mg, 0.70 mmol) afforded 245 mg (83%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 468 (M+1)

Analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>S:

Calcd: C, 66.8; H, 7.1; N, 9.0;

20 Found: C, 66.5; H, 7.1; N, 9.0.

Example 226.

**1-(4-Chloro-3-methylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

25 1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (315 mg, 1.00 mmol) and 4-chloro-3-methylbenzoic acid (171 mg, 1.00 mmol) afforded 240 mg (51%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 468 (M+1)

30 Analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>S:

Calcd: C, 69.3; H, 7.3; N, 9.0;

Found: C, 68.9; H, 7.2; N, 8.9.

**Example 227.**

**1-(5-Methylindole-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

5      1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (315 mg, 1.00 mmol) and 5-methylindole-2-carboxylic acid (263 mg, 1.50 mmol) afforded 240 mg (51%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 473 (M+1).

10

**Example 228.**

**1-(5-Methoxyindole-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

15      1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (315 mg, 1.00 mmol) and 5-methoxyindole-2-carboxylic acid (1.50 mmol) afforded 77 mg (16%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 489 (M+1)

Analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>S:

20      Calcd:    C, 69.3; H, 7.3; N, 9.0;  
              Found:    C, 68.9; H, 7.2; N, 8.9.

**Example 229.**

**1-(Benzothiazole-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

25      1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (315 mg, 1.00 mmol) and benzothiazole-2-carboxylic acid (200 mg, 1.12 mmol) afforded 180 mg (16%) of the title compound.

<sup>1</sup>NMR

30      IS-MS, m/e 477 (M-1)

**Example 230.****1-(5-Fluoroindole-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (315 mg,

5 1.00 mmol) and 5-fluoroindole-2-carboxylic acid (280 mg, 1.50 mmol) afforded 80 mg (17%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 477 (M+1)

Analysis for C<sub>28</sub>H<sub>33</sub>FN<sub>4</sub>O<sub>2</sub>·H<sub>2</sub>O:

10 Calcd: C, 68.0; H, 7.1; N, 11.3;

Found: C, 68.0; H, 6.7; N, 11.1.

**Example 231.****1-(Naphthalene-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (315 mg, 1.00 mmol) and naphthalene-2-carboxylic acid (220 mg, 1.28 mmol) afforded 160 mg (38%) of the title compound.

<sup>1</sup>NMR

20 IS-MS, m/e 470 (M+1)

Analysis for C<sub>30</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>·0.5 H<sub>2</sub>O:

Calcd: C, 75.3; H, 7.6; N, 8.8;

Found: C, 75.6; H, 7.4; N, 8.9.

**Example 232.****1-(6-Methoxyindole-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

Using Coupling Method C, 1-(D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine (315 mg, 1.00 mmol) and 6-methoxyindole-2-carboxylic acid (191 mg, 1.00 mmol) afforded 200 mg (41%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 489 (M+1)

Analysis for C<sub>29</sub>H<sub>36</sub>N<sub>4</sub>O<sub>3</sub>·0.5 H<sub>2</sub>O:

Calcd: C, 70.0; H, 7.5; N, 11.3;

Found: C, 69.3; H, 7.5; N, 11.1.

5

**Example 233.**

**1-(5-Chloroindole-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

Using Coupling Method A, 1-(D-phenylglycanyl)-1'-methyl-

10 4,4'-bispiperidine (315 mg, 1.00 mmol) and 5-chloroindole-2-carboxylic acid (230 mg, 1.15 mmol) afforded 220 mg (45%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 493 (M+1)

15 Analysis for C<sub>28</sub>H<sub>33</sub>ClN<sub>4</sub>O<sub>2</sub>·0.75 H<sub>2</sub>O:

Calcd: C, 66.4; H, 6.9; N, 11.1;

Found: C, 66.8; H, 6.6; N, 10.9.

**Example 234.**

20 **1-(3-Hydroxybenzoyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycanyl)-1'-methyl-4,4'-bispiperidine (200 mg, 0.635 mmol) and 3-benzyloxybenzoic acid (158 mg, 0.698 mmol) afforded 100 mg (30%) of 1-(3-benzyloxybenzoyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine. A solution of this material and 10% Pd/C in 3 mL of EtOH was treated with hydrogen gas (1 atm). After 16 h, the mixture was filtered, concentrated, and the residue triturated with EtOAc, affording 27 mg (32%) of the title compound.

30 <sup>1</sup>NMR

IS-MS, m/e 436 (M+1).

**Example 235.****1-(3-Hydroxy-4-methylbenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 5 0.635 mmol) and 3-acetoxy-4-methylbenzoic acid (135 mg, 0.698 mmol) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by column chromatography (4% to 6% 2 N NH<sub>3</sub> in methanol:-methylene chloride), 132 mg (46%) of the title compound.

10 <sup>1</sup>NMR

IS-MS, m/e 450 (M+1).

Analysis for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>·0.5 H<sub>2</sub>O:

Calcd: C, 71.4; H, 7.9; N, 9.3;

Found: C, 71.4; H, 7.9; N, 9.2.

15

The protected starting acid for the above procedure was prepared as follows:

**3-Acetoxy-4-methylbenzoic acid**

20 A solution of 3-hydroxy-4-methylbenzoic acid (3.0 g, 19.7 mmol) in acetic anhydride (5.6 mL) was treated with sulfuric acid (0.03 mL), heated to 70 °C, cooled and diluted with water. The resulting solid was collected by filtration yielding 1.14 g (30%) of the title compound, which was used 25 without further purification.

<sup>1</sup>NMR**Example 236.****1-(2-Hydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 30 0.635 mmol) and 2-acetoxybenzoic acid (125 mg, 0.698 mmol;

prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by column chromatography, 100 mg (36%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 436 (M+1).

**Example 237.**

10 **1-(4-Chloro-3-hydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (200 mg, 0.635 mmol) and 4-chloro-3-acetoxybenzoic acid (150 mg, 0.698 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by column chromatography, 110 mg (37%) of the title compound.

<sup>1</sup>NMR

20 IS-MS, m/e 470 (M+1).

**Example 238.**

**1-(4-Chloro-2-hydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

25 1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (200 mg, 0.635 mmol) and 4-chloro-2-acetoxybenzoic acid (150 mg, 0.698 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by radial chromatography, 60 mg (20%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 470 (M+1).

**Example 239.**

**1-(4-Chloro-3-methoxybenzoyl-D-phenylglycinyl)-1'-methyl-**

**5 4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (200 mg, 0.635 mmol) and 4-chloro-2-methoxybenzoic acid (130 mg, 0.698 mmol) afforded, after purification by column chromatography, 120 mg (39%) of the title compound.

**10 <sup>1</sup>NMR**

IS-MS, m/e 484 (M+1)

Analysis for C<sub>27</sub>H<sub>34</sub>ClN<sub>3</sub>O<sub>3</sub>:

Calcd: C, 67.0; H, 7.1; N, 8.7;

Found: C, 66.8; H, 7.1; N, 8.8.

**15**

**Example 240.**

**1-(3-Hydroxy-4-methoxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (200 mg, 0.635 mmol) and 3-acetoxy-4-methoxybenzoic acid (146 mg, 0.698 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by column chromatography, 52 mg (18%) of the title compound.

**16 <sup>1</sup>NMR**

IS-MS, m/e 466 (M+1).

**Example 241.**

**30 1-(2,4-Dihydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine (200 mg, 0.635 mmol) and 2,4-diacetoxybenzoic acid (167 mg, 0.698 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) 5 afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by column chromatography, 145 mg (50%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 452 (M+1).

10 Analysis for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>·0.75 H<sub>2</sub>O:

Calcd: C, 67.2; H, 7.5; N, 9.0;

Found: C, 67.3; H, 7.2; N, 9.3.

**Example 242.**

15 1-(2-Hydroxy-4-methoxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine (200 mg, 0.635 mmol) and 2-acetoxy-4-methoxybenzoic acid (146 mg, 0.698 mmol; prepared using methods substantially equivalent 20 to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by ion exchange chromatography (Varian, SCX), 118 mg (40%) of the title compound.

25 <sup>1</sup>NMR

IS-MS, m/e 466 (M+1).

Analysis for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>4</sub>·0.50 H<sub>2</sub>O:

Calcd: C, 68.3; H, 7.7; N, 8.9;

Found: C, 68.2; H, 7.4; N, 9.1.

**Example 243.****1-(5-Chloro-2-hydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (200 mg, 5 0.635 mmol) and 2-acetoxy-5-chlorobenzoic acid (150 mg, 0.698 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the crude acylation mixture with methanolic potassium carbonate and purification by ion exchange chromatography (Varian, SCX), 100 mg (33%) of the title compound.

 **$^1\text{NMR}$** 

IS-MS, m/e 471 (M+1).

Analysis for  $\text{C}_{26}\text{H}_{32}\text{ClN}_3\text{O}_3 \cdot 0.25 \text{ H}_2\text{O}$ :

15 Calcd: C, 65.8; H, 6.9; N, 8.9;  
Found: C, 65.9; H, 7.0; N, 9.2.

**Example 244.****1-(3-Chloro-4-hydroxybenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bispiperidine (315 mg, 20 1.00 mmol) and 4-acetoxy-3-chlorobenzoic acid (321 mg, 1.50 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the acylation mixture with methanolic potassium carbonate, 50 mg (27%) of the title compound.

 **$^1\text{NMR}$** 

IS-MS, m/e 470 (M+1).

30 Analysis for  $\text{C}_{26}\text{H}_{32}\text{ClN}_3\text{O}_3 \cdot 1.0 \text{ H}_2\text{O}$ :

Calcd: C, 64.0; H, 7.0; N, 8.6;  
Found: C, 63.7; H, 7.0; N, 8.7.

**Example 245.****1-(3-Hydroxynaphthalene-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

5    1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (315 mg, 1.00 mmol) and 3-acetoxynaphthalene-2-carboxylic acid (300 mg, 1.30 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the acylation product  
10    with methanolic potassium carbonate, 128 mg (38%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 486 (M+1).

15    **Example 246.**

**1-(6-Hydroxynaphthalene-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

1-(D-Phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (315 mg, 1.00 mmol) and 6-acetoxynaphthalene-2-carboxylic acid (300 mg, 1.30 mmol; prepared using methods substantially equivalent to those described for 3-acetoxy-4-methylbenzoic acid) afforded, after treatment of the acylation product with methanolic potassium carbonate, 210 mg (43%) of the title compound.

25    <sup>1</sup>NMR

IS-MS, m/e 486 (M+1).

Analysis for C<sub>30</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>·1.0 H<sub>2</sub>O:

Calcd:    C, 71.6; H, 7.4; N, 8.3;

Found:    C, 71.5; H, 7.3; N, 8.3.

30

**Examples 247-251.**

**Preparation of Starting Materials**

**1-(Benzylloxycarbonyl-D-phenylglycanyl)piperidine-4-methanol**

Using Coupling Method C, benzylloxycarbonyl-D-phenylglycine

(8.41 g, 29.5 mmol) and 4-piperidinemethanol (3.85 g, 37.4

5 mmol) afforded 10.2 g (93%) of the title compound.

<sup>1</sup>NMR

**1-(D-Phenylglycanyl)piperidine-4-methanol**

Using Deprotection Method C, 1-(benzylloxycarbonyl-D-

10 phenylglycanyl)piperidine-4-methanol (3.93 g, 29.5 mmol) and

10% palladium on carbon (1.30 g) afforded 2.31 g (88%) of

the title compound.

<sup>1</sup>NMR

IS-MS, m/e 249 (M+1).

15

**1-(4-Methoxybenzoyl-D-phenylglycanyl)piperidine-4-methanol**

Using methods substantially equivalent Acylation Method C

described prior to Example 201, 1-(D-phenylglycanyl)-

piperidine-4-methanol (1.23 g, 4.96 mmol) and p-anisoyl

20 chloride (0.888 g, 5.21 mmol) afforded, after purification by column chromatography (SiO<sub>2</sub>: 1:1 to 1:9 hexanes:EtOAc), 1.26 g (66%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 383 (M+1).

25

**1-(4-Methoxybenzoyl-D-phenylglycanyl)piperidine-4-carboxaldehyde**

A solution of 1-(4-methoxybenzoyl-D-phenylglycanyl)-

piperidine-4-methanol (0.800 g, 2.08 mmol) and N-methyl-

30 morpholine oxide (0.366 g, 3.13 mmol) in methylene chloride (15 mL) was treated with tetrapropylammonium perruthenate (TPAP, 2 mg). After 14 h, the mixture was treated with

additional TPAP (5 mg). After 20 h, the mixture was treated with additional TPAP (5 mg). After 32 h, the mixture was loaded directly onto a column and purified by column chromatography (SiO<sub>2</sub>: 1:1 to 1:4 hexanes:EtOAc) affording 5 0.286 g (36%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 381 (M+1).

**General Procedure:** Unless otherwise indicated, the product 10 of Examples 247-251 was obtained from the indicated amine and 1-(4-methoxybenzoyl-D-phenylglycanyl)piperidine-4-carboxaldehyde using Alkylation Method D.

**Example 247.**

15 **1-[(4-Methoxybenzoyl-D-phenylglycanyl)]-4-[(isopropylamino)-methyl]piperidine hydrochloride**  
1-(4-Methoxybenzoyl-D-phenylglycanyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and isopropylamine afforded, after treatment of the isolated product with 20 excess hydrochloric acid in methanol and concentration, 37 mg of the title compound as a hydrochloride salt.

<sup>1</sup>NMR

IS-MS, m/e 424 (M+1)

25 **Example 248.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[(dimethylamino)-methyl]piperidine**  
1-(4-Methoxybenzoyl-D-phenylglycanyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and dimethylamine 30 afforded 25 mg (47%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 410 (M+1)

**Example 249.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(N,N-diethyl-amino)methyl]piperidine hydrochloride**

5    1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and diethylamine afforded, after treatment of isolated product with excess hydrochloric acid in methanol and concentration, 42 mg of the title compound as a hydrochloride salt.

10     $^1\text{NMR}$

IS-MS, m/e 438 (M+1)

**Example 250.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(1-pyrrolidinyl)-methyl]piperidine**

15    1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and pyrrolidine afforded 27 mg (47%) of the title compound.

$^1\text{NMR}$

20    IS-MS, m/e 436 (M+1)

**Example 251.**

**1-[(4-Methoxybenzoyl-D-phenylglycinyl)]-4-[(3-pyrrolin-1-yl)methyl]piperidine hydrochloride**

25    1-(4-Methoxybenzoyl-D-phenylglycinyl)piperidine-4-carboxaldehyde (0.050 g, 0.131 mmol) and 3-pyrroline afforded, after treatment of isolated product with excess hydrochloric acid in methanol and concentration, 43 mg of the title compound as a hydrochloride salt.

30     $^1\text{NMR}$

IS-MS, m/e 434 (M+1)

**Examples 252 to 253****Preparation of Starting Materials****4- [(Benzylloxycarbonyl-D-phenylglycinyl)aminomethyl] -****5 piperidine**

Using Deprotection Method D, 4- [(benzylloxycarbonyl-D-phenylglycinyl)aminomethyl]-1-Boc piperidine (2.70 g, 5.61 mmol) afforded 1.56 g (73%) of the title compound.

<sup>1</sup>NMR

10 IS-MS, m/e 382 (M+1)

**4- [(Benzylloxycarbonyl-D-phenylglycinyl)aminomethyl] -1-  
cyclopentylpiperidine**

Using Alkylation Method D, 4- [(benzylloxycarbonyl-D-phenylglycinyl)aminomethyl]piperidine (1.50 g, 3.93 mmol) and cyclopentanone afforded 3.48 g (91%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 450 (M+1)

20

**4- [(D-Phenylglycinyl)aminomethyl] -1-cyclopentylpiperidine**

Using a deprotection procedure similar to that described above for preparation of 1-(D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine, 4- [(benzylloxycarbonyl-D-phenylglycinyl)aminomethyl]-1-cyclopentylpiperidine (1.70 g, 3.78 mmol) afforded 0.75 g (63%) of the title compound.

<sup>1</sup>NMR

IS-MS, m/e 316 (M+1)

30 **General Procedure:** Using Coupling Method A, 4- [(D-phenylglycinyl)aminomethyl] -1-cyclopentylpiperidine was coupled with the indicated acid.

**Example 252.**

**4-[(5-Chloroindole-2-carbonyl-D-phenylglycanyl)aminomethyl]-1-cyclopentylpiperidine**

5    4-[(D-Phenylglycanyl)aminomethyl]-1-cyclopentylpiperidine (0.100 g, 0.317 mmol) and 5-chloroindole-2-carboxylic acid (0.075 g, 0.38 mmol) afforded 156 mg (98%) of the title compound.

<sup>1</sup>NMR

10    IS-MS, m/e 493 (M+1)

**Example 253.**

**4-[(3-Methylindole-6-carbonyl-D-phenylglycanyl)aminomethyl]-1-cyclopentylpiperidine**

15    4-[(D-Phenylglycanyl)aminomethyl]-1-cyclopentylpiperidine (0.100 g, 0.317 mmol) and 3-methylindole-6-carboxylic acid (0.067 g, 0.38 mmol) afforded 137 mg (91%) of the title compound.

<sup>1</sup>NMR

20    IS-MS, m/e 473 (M+1)

**Particular Analytical Methods for Examples 254-276:**

HPLC Analysis (Method A): Dynamax (trademark) C18, 60Å column. The elution system consisted of a linear gradient from 90:10(95% H<sub>2</sub>O, CH<sub>3</sub>CN) / (95% CH<sub>3</sub>CN, H<sub>2</sub>O) to (95% CH<sub>3</sub>CN, H<sub>2</sub>O) over 20 min, followed by (95% CH<sub>3</sub>CN, H<sub>2</sub>O) isocratic elution over 15 min. The flow rate was 1 mL/min. UV Detection was performed at 254 nm unless otherwise noted.

30    HPLC Analysis (Method B): Microsorb-MV (trademark) C8 (4.6 x 250 mm) column. The elution system consisted of a linear

gradient from 95:5 (2.5% TFA in H<sub>2</sub>O) : (2.5% TFA in acetonitrile) to 0:100 (2.5% TFA in H<sub>2</sub>O) : (2.5% TFA in acetonitrile) over 25 min at 30 °C and a flow rate of 1 mL/min. UV Detection was performed at 254 nm unless 5 otherwise noted.

HPLC Analysis (Method C): Dynamax (trademark), C18, 60Å column. The elution system consisted of a linear gradient from 95:5 (0.2% TFA in H<sub>2</sub>O) / (0.2% TFA in CH<sub>3</sub>CN) to 5:95 (0.2% TFA in H<sub>2</sub>O) / (0.2% TFA in CH<sub>3</sub>CN) over 20 min, followed by (0.2% TFA in CH<sub>3</sub>CN) isocratic elution over 15 min. The 10 flow rate was 1 mL/min. UV Detection was performed at 254 nm unless otherwise noted.

HPLC Analysis (Method D): Waters Symmetry (trademark), C18 (4.6 x 250 mm) column. The elution system consisted of a linear gradient from 95:5 (0.2% TFA in H<sub>2</sub>O) / (0.2% TFA in CH<sub>3</sub>CN) to 5:95 (0.2% TFA in H<sub>2</sub>O) / (0.2% TFA in CH<sub>3</sub>CN) over 20 min, followed by (0.2% TFA in CH<sub>3</sub>CN) isocratic over 15 20 min. The flow rate was 1 mL/min. UV Detection was performed at 254 nm unless otherwise noted.

HPLC Analysis (Method E): Microsorb-MV C18 (4.6 x 250 mm) column. The elution system consisted of a linear gradient 25 from 90:10 (2.5% TFA in H<sub>2</sub>O) : (2.5% TFA in acetonitrile) to 10:90 (2.5% TFA in H<sub>2</sub>O) : (2.5% TFA in acetonitrile) over 25 min at 30 °C and a flow rate of 1 mL/min. UV Detection was performed at 254 nm unless otherwise noted.

30 API-MS (atmospheric pressure chemical ionization mass spectra) were obtained on a PE Sciex (trademark) API 150EX

with a heated nebulizer and nitrogen as the reagent gas in positive ion mode.

**Examples 254 to 257**

**5 Preparation of Starting Materials**

(R) - (-) -Boc-phenylglycinol: Di-tert-butyl dicarbonate (232.4 g, 1.06 mol) was added to a well stirred, ice bath cooled mixture of (R) - (-) -2-phenylglycinol (121.7 g, 0.887 mol), potassium carbonate (171.7 g, 1.24 mol), 1,4-dioxane (1 L), and water(1 L). The temperature rose from 5 °C - 11 °C during the addition. The reaction was allowed to stir overnight. The reaction was diluted with water (1 L), and cooled in ice-water. The resultant precipitate was collected by vacuum filtration, washed with water, air dried, and vacuum dried at 40 °C overnight to afford 201.7 g (95%) as a white solid.

1H-NMR (CDCl<sub>3</sub>)

TLC R<sub>f</sub> = 0.45 (83% CH<sub>2</sub>Cl<sub>2</sub>, EtOAc)

20

**(R) - (-) - [2- [(Methylsulphonyl)oxy] -1-phenylethyl] carbamic acid 1,1-dimethylethyl ester**

The sulphonate was prepared from the above alcohol according to J. Med. Chem. 1994, 37, 1819.

25 1H-NMR (CDCl<sub>3</sub>)

TLC R<sub>f</sub> = 0.45 (95% CH<sub>2</sub>Cl<sub>2</sub>, EtOAc)

**(R) -2- [(Butoxycarbonyl)amino] -2-phenylethyl azide**

The azide was prepared form the above sulphonate according to J. Med. Chem. 1994, 37, 1819.

30 1H-NMR (CDCl<sub>3</sub>)

TLC R<sub>f</sub> = 0.85 (95% CH<sub>2</sub>Cl<sub>2</sub>, EtOAc)

**(R) -2- (4-Methoxybenzoylamino) -2-phenylethyl azide**

(R) -2- [(Butoxycarbonyl)amino]-2-phenylethyl azide (47.8 g, 0.182 mole) was added to trifluoroacetic acid (500 mL) with 5 stirring and ice-water bath cooling. The cooling bath was removed, the reaction was allowed to stir 1 h, and the solvent was removed in vacuo at 35 °C water bath temperature. The residue was co-evaporated with toluene to give a weight of 75.0 g. The residue was dissolved in 10 1,4-dioxane (500 mL) and water (500 mL), with ice-water bath cooling, and then potassium carbonate (113.5 g, 0.82 mol), and anisoyl chloride (37.3 g, 0.219 mol) were added. Another portion of 1,4-dioxane (300 mL) was added to facilitate stirring. After stirring over the weekend, water 15 (1 L) was added. The mixture was cooled to -15 °C, and vacuum filtered to collect a white solid. The solid was washed with water, air dried, and then dried under vacuum at 50 °C for 4 h to afford 46.3 g (86%).

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

20 TLC R<sub>f</sub> = 0.85 (83% CH<sub>2</sub>Cl<sub>2</sub>, EtOAc)

**(R) -2- (4-Methoxybenzoylamino) -2-phenylethylamine**

(R) -2- (4-methoxybenzoylamino)-2-phenylethyl azide (46.3 g) was combined with 10% palladium on carbon in THF (400 mL), 25 methanol (100 mL) and was stirred under a hydrogen atmosphere. Analysis by TLC (70% methylene chloride, ethyl acetate) indicated absence of starting material after stirring overnight. The solution was filtered through diatomaceous earth, rinsed with THF, and evaporated. The 30 resulting solid was recrystallized with ethyl acetate, and dried under vacuum at 60 °C for 1 h to afford 35.4 g (84%) of a white crystalline solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

TLC R<sub>f</sub> = 0.17 (90% CH<sub>2</sub>Cl<sub>2</sub>, 9% Methanol, 1% NH<sub>4</sub>OH)

Examples 254-257 were prepared from (R)-2-(4-methoxybenzoyl-  
5 amino)-2-phenylethylamine and the indicated acid chloride  
using the acylation method described in Example 254  
(Acylation Method A).

**Example 254.**

10 (R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-4-methyl-  
benzamide

(Acylation Method A) p-Toluoyl chloride (0.22 mL, 1.6 mmol)  
was added via syringe to a 15 °C stirring mixture of (R)-2-  
(4-methoxybenzoylamino)-2-phenylethylamine (0.40 g, 1.48  
15 mmol), potassium carbonate (0.27 g, 1.9 mmol), 1,4-dioxane  
(8 mL), and water (4 mL). TLC analysis (80% methylene  
chloride, 18% methanol, 2% ammonium hydroxide) indicated  
reaction completion within 1 h. The solution was diluted  
with water, and the precipitated solid was collected by  
20 vacuum filtration. The precipitate was recrystallized from  
methanol and dried under vacuum at 50 °C overnight to afford  
the title compound (0.42 g, 72%) as a white solid.

<sup>1</sup>H-NMR (DMSO)

IS-MS, m/e = 389 (M+1)

25 Analysis for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>3</sub>:

Calcd: C, 74.21; H, 6.23; N, 7.21;

Found: C, 73.82; H, 6.32; N, 7.04.

HPLC Analysis (Method A): 99.3%, RT: 21.35 min.

Melting Point: 230-238 °C

**Example 255.**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-4-ethylbenzamide

Prepared from 4-ethylbenzoyl chloride (84%).

5 1H-NMR (DMSO)

IS-MS, m/e = 403 (M+1)

Analysis for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>:

Calcd: C, 74.60; H, 6.51; N, 6.96;

Found: C, 74.25; H, 6.63; N, 6.83.

10 HPLC Analysis (Method A): 95.4%, RT=22.62 min.

Melting Point: 222-229 °C

**Example 256.**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-4-isopropylbenzamide

Prepared from 4-isopropylbenzoyl chloride (40%).

1H-NMR (DMSO)

IS-MS, m/e = 417 (M+1)

Analysis for C<sub>26</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>:

20 Calcd: C, 74.97; H, 6.78; N, 6.73;

Found: C, 74.61; H, 6.78; N, 6.61.

HPLC Analysis (Method A): 98.4%, RT=23.77 min.

Melting Point: 239-244 °C

25 Example 257.

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-4-tert-butylbenzamide

Prepared from 4-tert-butylbenzoyl chloride (89%).

1H-NMR (DMSO)

30 IS-MS, m/e = 431 (M+1)

Analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub> · 0.25H<sub>2</sub>O:

Calcd: C, 74.54; H, 7.07; N, 6.44;

Found: C, 74.39; H, 7.13; N, 6.34.

HPLC Analysis (Method A): 96.4%, RT=25.04 min.

Melting Point = 171-175 °C

5 Examples 258 to 266

**Preparation of Starting Materials**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-tert-butoxycarbonylpiperidine-4-carboxamide.

10 N-Boc-iso-nipeptic acid (2.13 g, 9.5 mmol) followed by (R)-2-(4-methoxybenzoylamino)-2-phenylethylamine (2.34 g, 8.7 mmol) were added at 2 °C to a stirring mixture of EDCI (2.5 g, 13.0 mmol), and HOBT (1.64 g, 12.1 mmol) in DMF (50 mL). Triethylamine (1.8 mL, 13.0 mmol) was added dropwise. The reaction was allowed to warm to room temperature, with stirring overnight. Water (100 mL) was added, and the aqueous mixture was extracted with ethyl acetate (2 X 200 mL). The extracts were combined, and THF (200 mL) was added. Next, the organic layers were washed with water (5 X 70 mL), aqueous NaHCO<sub>3</sub> (70 mL), and brine (100 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The crude residue (4.2 g, 100%), was recrystallized from ethyl acetate and hexanes to afford 2.9 g (71%) of a white solid.

25 <sup>1</sup>H-NMR (DMSO)

IS-MS, m/e = 482 (M+1)

Analysis for C<sub>27</sub>H<sub>30</sub>N<sub>2</sub>O<sub>3</sub>:

Calcd: C, 67.34; H, 7.33; N, 8.73;

Found: C, 67.34; H, 7.46; N, 8.66.

30 HPLC Analysis (Method A): 98.8%, RT=20.72 min.

**(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]piperidine-4-carboxamide trifluoroacetate**

**(Deprotection Method A)** Trifluoroacetic acid was added to a stirring suspension of (R)-N-[2-(4-methoxybenzoylamino)-2-phenylethyl]-1-tert-butoxycarbonylpiperidine-4-carboxamide (2.0 g, 4.2 mmol), methylene chloride (20 mL), and anisole (0.5 g, 4.6 mmol) at room temperature. A solution was obtained and bubbling was observed. After 1 h, the reaction mixture was evaporated at 40 °C. The residue was taken up in warm methanol, and to this stirring solution was added ether to precipitate the product. The precipitate was collected by vacuum filtration, washed with ethyl acetate, then dried under vacuum at 60 °C overnight to afford 1.9 g (92%) of a white solid.

15    <sup>1</sup>H-NMR (DMSO)

IS-MS, m/e = 382 (M+1)

Analysis for C<sub>24</sub>H<sub>28</sub>F<sub>3</sub>N<sub>3</sub>O<sub>5</sub>:

Calcd:    C, 58.18; H, 5.70; N, 8.48;

Found:    C, 58.19; H, 5.78; N, 8.27.

20    HPLC Analysis (Method C): >99%, RT=20.40 min.

Except as otherwise noted, Examples 258-266 were prepared from (R)-N-[2-(4-methoxybenzoylamino)-2-phenylethyl]-piperidine-4-carboxamide trifluoroacetate and the indicated 25 aldehyde or ketone using the reductive alkylation method described in Example 258 (Alkylation Method A).

**Example 258.**

30    **(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-isopropyl-piperidine-4-carboxamide**

**(Alkylation Method A)** (R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]piperidine-4-carboxamide trifluoroacetate

(0.50 g, 1.0 mmol), acetone (4.5 mL, 61 mmol), acetic acid (0.28 mL, 4.9 mmol), and sodium cyanoborohydride (0.32 g, 5.1 mmol) were combined in methanol, and stirred. After 4 h, TLC (79% CH<sub>2</sub>Cl<sub>2</sub>, 19% methanol, 1% NH<sub>4</sub>OH) indicated reaction completion. The solution was diluted with methanol (100 mL), and passed through H<sup>+</sup> form ion exchange resin (Varian SCX cartridge, Catalog #1225-6035) washed with methanol, and then with 2 M NH<sub>3</sub> in methanol to collect the product. The product was recrystallized from methanol and ether to afford 0.30 g (70%) of a white crystalline solid.

1H-NMR (DMSO)

IS-MS, m/e = 424 (M+1)

Analysis for C<sub>25</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub>·0.75H<sub>2</sub>O:

Calcd: C, 68.70; H, 7.96; N, 9.61;

15 Found: C, 68.73; H, 7.68; N, 9.29.

HPLC Analysis (Method C): >99% RT=18.19 min.

Examples 259-262 were purified by passing a solution through a silica gel column, eluting with 200:10:1 methylene chloride, methanol, and concentrated ammonium hydroxide.

**Example 259.**

**(R)-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-cyclopentylpiperidine-4-carboxamide**

25 Prepared from cyclopantanone (44%).

1H-NMR (DMSO)

IS-MS, m/e = 450 (M+1)

Analysis for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>·0.25H<sub>2</sub>O:

Calcd: C, 71.42; H, 7.88; N, 9.25;

30 Found: C, 71.21; H, 7.93; N, 9.18.

HPLC Analysis (Method C): >99%, RT=18.84 min.

Melting Point = 253-257 °C

**Example 260.**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-cyclohexylpiperidine-4-carboxamide

5 Prepared from cyclohexanone (65%).

1H-NMR (DMSO)

IS-MS, m/e = 464 (M+1)

Analysis for C<sub>28</sub>H<sub>37</sub>N<sub>3</sub>O<sub>3</sub>·1.0H<sub>2</sub>O:

Calcd: C, 69.83; H, 8.16; N, 8.72;

10 Found: C, 69.64; H, 7.84; N, 8.90.

HPLC Analysis (Method C): >99%, RT=19.13 min.

Melting Point = 239-243 °C.

**Example 261.**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-ethyl-piperidine-4-carboxamide

Prepared from acetaldehyde (36%).

1H-NMR (DMSO)

IS-MS, m/e 410 (M+1)

20 Analysis for C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>:

Calcd: C, 70.39; H, 7.63; N, 10.26;

Found: C, 70.06; H, 7.67; N, 10.00.

HPLC Analysis (Method D): 96.9%, RT=16.04 min.

Melting Point = 245-251 °C.

25

**Example 262.**

(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-(1-methyl-piperidin-4-yl)piperidine-4-carboxamide

Prepared from 1-methylpiperid-4-one (27%).

30 1H-NMR (DMSO)

IS-MS, m/e 479 (M+1)

Analysis for C<sub>28</sub>H<sub>38</sub>N<sub>4</sub>O<sub>3</sub>·0.25H<sub>2</sub>O:

Calcd: C, 69.61; H, 8.03; N, 11.60;

Found: C, 69.72; H, 8.11; N, 11.48.

HPLC Analysis (Method D): 97.0%, RT=15.42 min.

Melting Point = 252-259 °C.

5

(No example for Examples 263-264.)

Examples 265-266 were purified by passing a solution through  
a silica gel column, eluting with 200:10:1 methylene

10 chloride, methanol, and concentrated ammonium hydroxide.

**Example 265.**

**(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-(3-pyridinylmethyl)piperidine-4-carboxamide**

15 Prepared from pyridine-3-carboxaldehyde (68%).

<sup>1</sup>H-NMR (DMSO)

CI-MS, m/e = 473 (M+1)

HPLC Analysis (Method D): 92.7%, RT=15.39 min.

20 **Example 266.**

**(R)-N-[2-(4-Methoxybenzoylamino)-2-phenylethyl]-1-(4-pyridinylmethyl)piperidine-4-carboxamide**

Prepared from pyridine-4-carboxaldehyde (63%).

<sup>1</sup>H-NMR (DMSO)

25 CI-MS, m/e = 473 (M+1)

HPLC Analysis (Method D): 89.2%, RT=15.33 min.

**Example 267.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-piperidinyl-  
30 methyl)piperazine trifluoroacetate**

**1- [D- (+) -Benzylloxycarbonylphenylglycanyl] - (4-tert-butoxy-carbonyl)piperazine.**

(Coupling Method A) D- (+) -Benzylloxycarbonylphenylglycine

(58.0 g, 203 mmol) and 1-Boc-piperazine (41.7 g, 224 mmol)

5 were dissolved in DMF (1 L) and cooled to approximately -15 °C in an ice-methanol bath. Diethyl cyanophosphonate (37.0 mL, 244 mmol) was slowly added to the mixture.

Triethylamine (59.4 mL, 426 mmol) was added dropwise to the solution. The mixture was stirred at -15 °C for 2 h and was

10 allowed to gradually warm to room temperature overnight.

The mixture was diluted with ethyl acetate and water. The

layers were separated, and the water layer extracted with ethyl acetate. The organic layers were combined, washed

with 10% citric acid (2 x 500 mL) and brine, dried ( $\text{Na}_2\text{SO}_4$ ),

15 filtered and concentrated under vacuum. The crude product was filtered through a plug of silica gel (1.2 kg) using 1:1 hexanes:ethyl acetate as eluent to provide 1- [D- (+) -benzyl-oxycarbonylphenylglycanyl] -4- (tert-butoxycarbonyl)piperazine (69.9 g, 76%) as a colorless oil.

20  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

API-MS, m/e = 454 (M+1)

**1- [D- (+) -Phenylglycanyl] -4- (tert-butoxycarbonyl)piperazine**

1- [D- (+) -Benzylloxycarbonylphenylglycanyl] -4- (tert-butoxy-carbonyl)piperazine (69.5 g, 153 mmol) was dissolved in ethanol (500 mL). The mixture was degassed with nitrogen and Pd/C (6.8 g) was added. Hydrogen was bubbled through the mixture for 1 h, and it was maintained under a hydrogen atmosphere for 16 h. The Pd/C was removed by filtration through cellulose powder. The filter cake was rinsed with ethanol and ethyl acetate. The filtrate was concentrated under vacuum to give 1- [D- (+) -phenylglycanyl] -4- (tert-

butoxycarbonyl)piperazine (45.3 g, 93%) as a light yellow solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

API-MS, m/e = 320 (M+1)

5

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(tert-butoxy-carbonyl)piperazine**

(Acylation Method B) 1-[D-(+)-phenylglycanyl]-4-(tert-butoxycarbonyl)piperazine (42.0 g, 131.5 mmol) was dissolved  
10 in 1,4-dioxane (420 mL) and water (210 mL) and was cooled to 10 °C. Potassium carbonate (36.4 g, 263 mmol) was added, followed by p-anisoyl chloride (24.7 g, 144 mmol). The mixture was stirred at room temperature overnight. The mixture was diluted with water and ethyl acetate. The  
15 layers were separated, and the water layer extracted with ethyl acetate. The organic layers were combined, washed with brine, dried, filtered and concentrated to provide 1-(4-methoxybenzoyl-D-phenylglycanyl)-(4-tert-butoxy-carbonyl)piperazine (58.7 g, 98%) as an off-white solid.

20 <sup>1</sup>H-NMR (CDCl<sub>3</sub>)

API-MS, m/e = 454 (M+1)

**1-(4-Methoxybenzoyl-D-phenylglycanyl)piperazine**

**trifluoroacetate**

25 1-(4-Methoxybenzoyl-D-phenylglycanyl)-(4-tert-butoxy-carbonyl)piperazine (20.0 g, 44.1 mmol) was dissolved in dichloromethane (50 mL) and anisole (20 mL). To this vigorously stirred mixture was added trifluoroacetic acid (50 mL). The mixture was stirred for 25 min at room  
30 temperature. The solvents were removed under vacuum. The residue was triturated in ether and sonicated for 60 min. The solid was collected by filtration and dried in a vacuum

pistol overnight to provide 1-(4-methoxybenzoyl-D-phenyl-glycinyl)piperazine trifluoroacetate (18.2 g, 88%) as a light yellow solid.

<sup>1</sup>H-NMR (CD<sub>3</sub>OD)

5 API-MS, m/e = 354 (M+1)

**1-Boc-isonipecotic acid**

Isonipecotic acid (15.0 g, 116 mmol) was dissolved in THF (300 mL), water (150 mL) and 6 N NaOH (40 mL). Di-tert-butyl dicarbonate (26.6 g, 122 mmol) was added and the mixture stirred overnight. The mixture was diluted with water and ethyl acetate, and the layers separated. The water layers were extracted with ethyl acetate, and the organic layers discarded. The water layer was diluted with KHSO<sub>4</sub> (2 N, pH~4) and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to provide 1-Boc-isonipecotic acid (23.9 g, 90%) as a white solid.

<sup>1</sup>H-NMR (CDCl<sub>3</sub>)

20 API-MS, m/e = 230 (M+1)

**1-Boc-piperidine-4-methanol**

1-Boc-isonipecotic acid (10.0 g, 214 mmol) was dissolved in THF (400 mL) and cooled to 0 °C. A solution of BH<sub>3</sub>·THF (180 mL, 1 N in THF, 180 mmol) was added slowly. The mixture stirred for 1 h at 0 °C and was allowed to warm to room temperature for 12 h. The mixture was carefully quenched with water and diluted with ethyl acetate. The water layer was extracted with ethyl acetate. The organic layers were combined, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to provide 1-Boc-piperidine-4-methanol (7.98 g, 85%) as a white solid.

1H-NMR (CDCl<sub>3</sub>)

API-MS, m/e = 220 (M+1)

**1-Boc-piperidine-4-carboxaldehyde**

5 Dimethyl sulfoxide (3.5 mL, 48.7 mmol) was dissolved in dichloromethane (100 mL) and was cooled to -78 °C. Oxalyl chloride (3.65 mL, 41.8 mmol) was added. The mixture stirred for 30 min. To this solution was added a solution of 1-Boc-piperidine-4-methanol (7.5 g, 34.8 mmol) in  
10 dichloromethane (15 mL), and the mixture stirred for 1 h. Triethylamine (9.7 mL, 69.6 mmol) was added slowly and the mixture stirred at -78 °C for 30 min and warmed to room temperature over the course of 1 h. The mixture was diluted with water and the layers separated. The water layer was  
15 extracted with dichloromethane and the organic layers combined, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated to provide 1-Boc-piperidine-4-carboxaldehyde (6.75 g, 91%) as a yellow oil.

1H-NMR (CDCl<sub>3</sub>)

20 API-MS, m/e = 214 (M+1)

**1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine**

(Alkylation Method B) Using Alkylation Method A, except  
25 using sodium triacetoxyborohydride in 1,2-dichloroethane, 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-(1-Boc-piperidin-4-ylmethyl)piperazine was prepared from 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine trifluoroacetate and 1-Boc-piperidine-4-carboxaldehyde (85%).

30 1H-NMR (CDCl<sub>3</sub>)

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-piperidinylmethyl)piperazine trifluoroacetate.**

Using Deprotection Method A, the title compound was prepared from 1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(1-Boc-5-piperidin-4-ylmethyl)piperazine (90%).

Melting Point = 70-72 °C with decomposition

IR (KBr)

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

API-MS, m/e = 451 (M+1)

10 Analysis for  $\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_3 \cdot 2.5\text{TFA} \cdot 0.4\text{H}_2\text{O}$ :

Calcd: C, 50.12; H, 5.06; N, 7.54;

Found: C, 49.81; H, 5.33; N, 7.39.

HPLC Analysis (Method B): 97.1% RT=14.3 min.

15 **Examples 268 to 272**

Unless otherwise indicated, using Alkylation Method A or B, the title compounds were prepared from 1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(4-piperidinylmethyl)piperazine trifluoroacetate and the indicated aldehyde or ketone.

20

**Example 268.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(1-methylpiperidin-4-ylmethyl)piperazine hydrochloride**

Prepared from paraformaldehyde using Method A (56%).

25 IR (KBr)

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

CI-MS, m/e = 465 (M+1)

**Example 269.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(1-isopropyl-5-piperidin-4-ylmethyl)piperazine hydrochloride**

Prepared from acetone using Method A (72%).

Melting Point = 172-180 °C with decomposition

IR (KBr)

$^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

CI-MS, m/e = 493 (M+1)

5 Analysis for  $\text{C}_{29}\text{H}_{40}\text{N}_4\text{O}_3 \cdot 3\text{HCl}$ :

Calcd: C, 55.85; H, 7.34; N, 8.98;

Found: C, 55.63; H, 7.32; N, 8.66.

HPLC Analysis (Method B): 98.2% RT=14.4 min.

10 Example 270.

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[3-(3-pyridinyl)-propyl]piperazine hydrochloride**

Prepared from pyridine-3-propionaldehyde (prepared as described below) using Method B (72%).

15  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

CI-MS, m/e = 473 (M+1)

**Pyridine-3-propionaldehyde**

(Oxidation Method A) 1,1,1-Triacetoxy-1,1-dihydro-1,2-

20 benziodoxol-3(1H)-one (5.4 g, 12.7 mmol) was suspended in dichloromethane (45 mL). 3-Pyridinepropanol (1.59 g, 11.6 mmol) as a solution in dichloromethane (35 mL) was added slowly. The mixture stirred for 3 h at room temperature. The mixture was diluted with saturated aqueous  $\text{NaHCO}_3$  and ether. The mixture was stirred for 10 min and was diluted with sodium thiosulfate (2 N) and stirred until the solids dissolved. The layers were separated, and the water layer was extracted with ether. The organic layers were combined, washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to provide pyridine-3-propionaldehyde (1.03 g, 66%) as a yellow oil.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

**Example 271.**

**1- (4-Methoxybenzoyl-D-phenylglycanyl)-4-[3-(4-pyridinyl)-propyl]piperazine hydrochloride.**

5 Prepared from pyridine-4-propionaldehyde (prepared as described below) using Method A; the hydrochloride salt was prepared using HCl (2 M) in diethyl ether (76%).

1H-NMR (CD<sub>3</sub>OD)

CI-MS, m/e = 473 (M+1)

10

**Pyridine-4-propionaldehyde**

Prepared from 4-pyridinepropanol using Oxidation Method A (80%).

1H-NMR (CDCl<sub>3</sub>)

15

**Example 272.**

**1- (4-Methoxybenzoyl-D-phenylglycanyl)-4-(2-cyclopentyl-ethyl)piperazine hydrochloride hydrate**

The free base was prepared from cyclopentylacetaldehyde 20 (prepared as described below) using Method B (58%).

1H NMR (CDCl<sub>3</sub>)

To a stirred solution of 1-(4-methoxybenzyl-D-phenyl-glycanyl)-4-(2-cyclopentylethyl)piperazine (260 mg, 0.58 mmol) in ether (10 mL) and methylene chloride (1 mL) was 25 added hydrogen chloride as a 2 N solution in ether (about 2 mL), and the resulting precipitate was filtered to give 1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(2-cyclopentyl-ethyl)piperazine hydrochloride as a pale yellow solid.

1H NMR (CD<sub>3</sub>OD)

30 IS-MS, m/e = 450 (M+1)

Analysis for C<sub>27</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>·HCl·0.5H<sub>2</sub>O:

Calcd: C, 65.51; H, 7.53; N, 8.49;

Found: C, 65.67; H, 7.58; N, 8.13.

HPLC Analysis (Method E): >99%, RT=15.84

Melting Point = 190-192 °C

5 **Cyclopentylacetaldehyde**

Using Oxidation Method A, the title compound was prepared from 2-cyclopentylethanol and used with trace amounts of ether and methylene chloride present due to volatility of product.

10 **1H NMR (CDCl<sub>3</sub>)**

**Example 273.**

**1- (4-Methoxybenzoyl-D-phenylglycanyl)-4-(3-pyrrolidinyl)-piperazine trifluoroacetate.**

15

**(R) - (+)-1-Boc-3-pyrrolidinol**

To a stirred solution of (R) - (+)-3-pyrrolidinol (2 g, 22.96 mmol) in tetrahydrofuran (60 mL) and water (30 mL) was added di-tert-butyl dicarbonate (5.27 g, 24.15 mmol) and 3 N sodium hydroxide (16 mL), and the resulting solution was stirred for 6 h. Another portion of di-tert-butyl dicarbonate (0.74 g, 0.34 mmol) was added and the solution was stirred overnight. The reaction was diluted with water (40 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were washed with 2 N potassium hydrogen sulfate (200 mL), saturated sodium bicarbonate (2 x 150 mL), brine (150 mL) and dried over magnesium sulfate. Removal of solvent *in vacuo* gave (R) - (+)-1-Boc-3-pyrrolidinol (4.21 g, 98%) as a yellow oil.

30 **1H-NMR (CDCl<sub>3</sub>)**

**1-Boc-3-pyrrolidinone**

Using Oxidation Method A, the title compound was prepared from (R)-(+)-1-Boc-3-pyrrolidinol (85%).

1H NMR (CDCl<sub>3</sub>)

5   **1-(4-Methoxybenzyl-D-phenylglycanyl)-4-(1-Boc-3-pyrrolidinyl)piperazine**

Using Alkylation Method B, the title compound was prepared (69%) from 1-(4-methoxybenzyl-D-phenylglycanyl)piperazine trifluoroacetate and 1-Boc-3-pyrrolidinone.

10   1H NMR (CDCl<sub>3</sub>)

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(3-pyrrolidinyl)-piperazine trifluoroacetate.**

Using Deprotection Method A, the title compound was prepared  
15   from 1-(4-methoxybenzyl-D-phenylglycanyl)-4-(1-Boc-3-pyrrolidinyl)piperazine.

1H NMR (CD<sub>3</sub>OD)

**Example 274.**

20   **1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[2-(4-pyridinyl)-ethyl]piperazine**

**1-Boc-4-[2-(4-pyridinyl)ethyl]piperazine**

25   1-Boc-piperazine (4.0 g, 21.5 mmol), 4-vinylpyridine (2.94 g, 27.9 mmol), and acetic acid (1.29 g, 21.5 mmol) were mixed in ethanol and heated to reflux for 48 h. The mixture was cooled to room temperature and concentrated under vacuum to provide 1-Boc-4-[2-(4-pyridinyl)ethyl]-piperazine (2.9 g, 45%) as an off white solid. The product  
30   was used without further purification.

1H-NMR(CDCl<sub>3</sub>)

CI-MS, m/e = 292 (M+1)

**1-[2-(4-Pyridinyl)ethyl]piperazine hydrochloride**

(Deprotection Method B) 1-Boc-4-[2-(4-pyridinyl)ethyl]-piperazine (1.0 g, 3.43 mmol) was dissolved in ethyl ether.

5 Ethyl acetate (15 mL) saturated with HCl was added, and the mixture stirred for 30 min at room temperature. The mixture was concentrated under vacuum and provided 1-[2-(4-pyridinyl)ethyl]piperazine hydrochloride (900 mg, 87%) as a tan solid.

10  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

CI-MS, m/e = 192 (M+1)

**1-(D-Boc-phenylglycanyl)-4-[2-(4-pyridinyl)ethyl]piperazine**

Using Coupling Method A, the title compound was prepared  
15 from 1-[2-(4-pyridinyl)ethyl]piperazine and Boc-D-phenylglycine (95%).

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )

CI-MS, m/e = 425 (M+1)

20 **1-(D-Phenylglycanyl)-4-[2-(4-pyridinyl)ethyl]piperazine hydrochloride**

Using Deprotection Method B, the title compound was prepared from 1-(D-Boc-phenylglycanyl)-4-[2-(4-pyridinyl)ethyl]-piperazine (89%).

25  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ )

CI-MS, m/e = 325 (M+1)

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[2-(4-pyridinyl)-ethyl]piperazine**

30 Using Acylation Method B, the title compound was prepared from 1-(D-phenylglycanyl)-4-[2-(4-pyridinyl)ethyl]piperazine hydrochloride and p-anisoyl chloride (70%).

1H-NMR (CDCl<sub>3</sub>)

CI-MS, m/e = 459 (M+1)

HPLC Analysis (Method E): 99.7%, RT=10.98 min.

5   **Examples 275 to 276**

Using Alkylation Method B, the title compounds were prepared from 1-(4-methoxybenzoyl-D-phenylglycanyl)-4-(3-pyrrolidinyl)piperazine trifluoroacetate and the indicated aldehyde or ketone.

10

**Example 275.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(1-methylpyrrolidin-3-yl)piperazine**

Prepared from paraformaldehyde (20%).

15

1H-NMR (CDCl<sub>3</sub>)

**Example 276.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(1-isopropyl-pyrrolidin-3-yl)piperazine.**

20

Prepared from acetone (59%).

1H-NMR (CDCl<sub>3</sub>)

The following analytical methods apply to Examples 277-336.

25

Analytical RPHPLC Method 1 = Vydac C18, linear gradient of 90/10 - 50/50 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min.

30

Analytical RPHPLC Method 2 = Vydac C18, linear gradient of 85/20 - 40/60 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min.

**Examples 277 to 290**

Unless otherwise indicated, the products of Examples 277 through 290 were obtained from the indicated acid and 1-D-phenylglycinyl-1'-methyl-4,4'-bispiperidine using the 5 procedure described in Example 277 (Coupling Method B).

**Example 277.****1-(2-Chloropyridine-5-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

10 (Coupling Method B) To a stirring solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.20 g, 1.0 mmol) and 1-hydroxybenzotriazole hydrate (0.15 g, 1.1 mmol) in DMF (3 mL) was added 2-chloropyridine-5-carboxylic acid (0.14 g, 0.89 mmol) followed by a solution 15 of 1-D-phenylglycinyl-1'-methyl-4,4'-bispiperidine (0.25 g, 0.80 mmol) in DMF (2 mL). After stirring for 18 h, the solvent was removed in vacuo and the residue was partitioned between dichloromethane and 1 N sodium hydroxide. The aqueous phase was separated, extracted twice with 20 dichloromethane, and the combined organic phases were dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo. The resulting solid was dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with 10% methanol (containing 2 N ammonia) in 25 dichloromethane through 15% methanol (containing 2 N ammonia) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 0.258 g (71%) of a white solid.

## 1H-NMR

30 IS-MS, m/e 455.0 (M+1)

Analysis for C<sub>25</sub>H<sub>31</sub>N<sub>4</sub>O<sub>2</sub>Cl·0.4H<sub>2</sub>O:

Calcd: C, 64.96; H, 6.93; N, 12.13;

Found: C, 64.68; H, 6.72; N, 12.02.

Analytical RPHPLC, Method 1, RT = 21.28 min (98%)

**Example 278.**

5 **1-(5-Chloropyridine-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 2-chloropyridine-5-carboxylic acid (61%).

1H-NMR

IS-MS, m/e 454.9 (M+1)

10 Analysis for C<sub>25</sub>H<sub>31</sub>N<sub>4</sub>O<sub>2</sub>Cl·0.4H<sub>2</sub>O:

Calcd: C, 64.96; H, 6.93; N, 12.12;

Found: C, 64.75; H, 6.64; N, 12.00.

Analytical RPHPLC, Method 1, RT = 27.23 min (100%)

15 **Example 279.**

**1-(3-Cyano-4-fluorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 3-cyano-4-fluorobenzoic acid (66%).

1H-NMR

20 IS-MS, m/e 463.0 (M+1)

Analysis for C<sub>27</sub>H<sub>31</sub>N<sub>4</sub>O<sub>2</sub>F·0.3H<sub>2</sub>O:

Calcd: C, 69.30; H, 6.81; N, 11.97;

Found: C, 68.91; H, 6.58; N, 11.77.

25 Analytical RPHPLC [Vydac C18, linear gradient of 85/15 - 45/55 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min] RT = 21.54 (99%).

**Example 280.**

30 **1-(5-Chlorobenzo[b]thiophene-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 5-chlorobenzo[b]thiophene-2-carboxylic acid (38%).

1H-NMR

IS-MS, m/e 509.9 (M+1)

Analysis for C<sub>28</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub>SCl·0.3H<sub>2</sub>O:

Calcd: C, 65.24; H, 6.37; N, 8.15;

5 Found: C, 65.01; H, 6.12; N, 8.07.

Analytical RPHPLC, Method 1, RT = 36.08 min (99%)

**Example 281.**

1- (2-Benzo [b] thiophenecarbonyl-D-phenylglycanyl) -1' -methyl-

10 4,4' -bispiperidine

Prepared from 2-benzo [b] thiophenecarboxylic acid (82%).

1H-NMR

IS-MS, m/e 475.9 (M+1)

Analysis for C<sub>28</sub>H<sub>33</sub>N<sub>3</sub>O<sub>2</sub>S·0.4H<sub>2</sub>O:

15 Calcd: C, 69.65; H, 7.06; N, 8.70;

Found: C, 69.45; H, 6.90; N, 8.58.

Analytical RPHPLC, Method 2, RT = 22.30 min (100%)

**Example 282.**

20 1- (6-Chlorobenzo [b] thiophene-2-carbonyl-D-phenylglycanyl) -

1' -methyl-4,4' -bispiperidine

Prepared from 6-chlorobenzo [b] thiophene-2-carboxylic acid (77%).

1H-NMR

25 IS-MS, m/e 509.9 (M+1)

Analysis for C<sub>28</sub>H<sub>32</sub>N<sub>3</sub>O<sub>2</sub>SCl·0.3H<sub>2</sub>O:

Calcd: C, 65.24; H, 6.37; N, 8.15;

Found: C, 64.97; H, 6.23; N, 8.07.

Analytical RPHPLC, Method 2, RT = 27.62 min (100%)

**Example 283.**

**1-(Indole-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 2-indolecarboxylic acid (57%).

5     $^1\text{H-NMR}$

IS-MS, m/e 459.0 (M+1)

Analysis for  $\text{C}_{28}\text{H}_{34}\text{N}_4\text{O}_2 \cdot 0.4\text{H}_2\text{O}$ :

Calcd:    C, 71.10; H, 7.59; N, 11.85;

Found:    C, 70.82; H, 7.25; N, 11.74.

10    Analytical RPHPLC, Method 1, RT = 29.60 min (99%)

**Example 284.**

**1-(1-Methylindole-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

15    Prepared from 1-methylindole-2-carboxylic acid (43%).

$^1\text{H-NMR}$

IS-MS, m/e 473.0 (M+1)

Analytical RPHPLC, Method 2, RT = 22.20 min (98%)

20    **Example 285.**

**1-(Benzofuran-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 2-benzofurancarboxylic acid (50%).

$^1\text{H-NMR}$

25    IS-MS, m/e 460.0 (M+1)

Analytical RPHPLC, Method 1, RT = 27.59 min (100%)

**Example 286.**

**1-(3-Methylbenzofuran-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bis(piperidine)**

Prepared from 3-methylbenzofuran-2-carboxylic acid (47%).

$^1\text{H-NMR}$

IS-MS, m/e 474.1 (M+1)

Analytical RPHPLC, Method 1, RT = 31.31 min (95%)

**Example 287.**

5   **1-(5-Methylbenzofuran-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

Prepared from 5-methylbenzofuran-2-carboxylic acid (45%).

1H-NMR

IS-MS, m/e 474.3 (M+1)

10   Analytical RPHPLC, Method 1, RT = 30.91 min (100%)

**Example 288.**

**1-(6-Methoxybenzofuran-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

15   Prepared from 6-methoxybenzofuran-2-carboxylic acid (50%).

1H-NMR

IS-MS, m/e 490.0 (M+1)

Analytical RPHPLC, Method 1, RT = 29.26 min (100%)

20   **Example 289.**

**1-(5-Chlorobenzofuran-2-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

Prepared from 5-chlorobenzofuran-2-carboxylic acid (59%).

1H-NMR

25   IS-MS, m/e 493.9 (M+1)

Analysis for C<sub>28</sub>H<sub>32</sub>N<sub>3</sub>O<sub>3</sub>Cl·0.5H<sub>2</sub>O:

Calcd:   C, 66.85; H, 6.61; N, 8.35;

Found:   C, 66.46; H, 6.28; N, 8.25.

Analytical RPHPLC, Method 1, RT = 34.86 min (100%)

30

**Example 290.****1-(2-Aminobenzimidazole-5-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

Prepared from 2-amino-5-carboxybenzimidazole hydrochloride  
5 (32%).

**1H-NMR**

IS-MS, m/e 475.2 (M+1)

Analytical RPHPLC [Vydac C18, linear gradient of 98/2 -  
58/42 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40  
10 min, 1 mL/min] RT = 24.56 (90%).

**Example 291. 1-(3-Aminobenzisoxazole-5-carbonyl-D-phenylglycine)-1'-methyl-4,4'-bispiperidine**

To a stirring solution of acetoxime (98 mg, 7.1 mmol) in DMF  
15 (5 mL) was added a 1 M solution of potassium tert-butoxide  
(1.3 mL, 1.3 mmol) in THF. After 2 min, 1-(3-cyano-4-  
fluorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine  
(303 mg, 0.65 mmol) was added; and, after another hour, the  
solvent was partially removed and the residue was  
20 partitioned between brine and dichloromethane. The layers  
were separated and the aqueous phase was extracted another  
two times with dichloromethane. The combined organics were  
dried ( $MgSO_4$ ), filtered and concentrated in vacuo.

IS-MS, m/e 516.0 (M+1)

25 The residue was then dissolved in ethanol (3.6 mL) and 1 N  
HCl was added. The stirring solution was heated to reflux.  
After 5 h, the heating mantle was removed and after  
cooling, the solution was diluted ethyl acetate and water.  
30 The pH of the aqueous phase was adjusted to 11 with 2 N  
sodium hydroxide and extracted twice with dichloromethane.  
The combined dichloromethane extracts were dried ( $MgSO_4$ ),

filtered and concentrated in vacuo. The resulting solid was dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with 2% methanol (containing 2 N ammonia) in dichloromethane through 10%  
5 methanol (containing 2 N ammonia) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 89 mg (29%) of an off-white solid.

<sup>1</sup>H-NMR

IS-MS, m/e 476.3 (M+1)

10 Analytical RPHPLC, Method 1, RT = 19.55 min (99%)

#### Examples 292 to 303

#### Preparation of Starting Materials

15 **1-(Boc-D-phenylglycyl)-4-hydroxypiperidine**  
**(Coupling Method C)** To a stirring solution of 1-hydroxy-7-azabenzotriazole (10.24 g, 75.2 mmol) and EDCI (14.42 g, 75.2 mmol) in DMF (160 mL) was added a solution of Boc-D-phenylglycine (18.9 g, 75.2 mmol) in DMF (80 mL). After  
20 10 min, 4-hydroxypiperidine (6.85 g, 67.7 mmol) was added. After stirring over night, the solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and water. The organic phase separated and washed with saturated aqueous NaHCO<sub>3</sub>, followed by brine, dried over  
25 MgSO<sub>4</sub>, filtered and concentrated in vacuo. Two-thirds of this material was dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with a gradient of dichloromethane through 1:1 dichloromethane/ethyl acetate. The product containing  
30 fractions were combined and concentrated in vacuo to give 15.71 g (94%) of a white foam.

<sup>1</sup>H-NMR

IS-MS, m/e 335.1 (M+1)

Analysis for C<sub>18</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>:

Calcd: C, 64.65; H, 7.84; N, 8.37;

Found: C, 64.40; H, 7.77; N, 8.12.

5

**1-(D-phenylglycinyl)-4-hydroxypiperidine**

(Deprotection Method D) To a stirring solution of 1-(Boc-D-phenylglycinyl)-4-hydroxypiperidine (5 g, 15 mmol) in dichloromethane (290 mL) was added anisole, (8 mL) followed by trifluoroacetic acid (29 mL). After stirring for 4 h, the solvent was concentrated in vacuo and the residue was suspended with stirring in diethyl ether. After 1 h, the mixture was filtered and the solid was partitioned between ethyl acetate and saturated aqueous NaHCO<sub>3</sub>. The organic phase was washed with brine, dried with MgSO<sub>4</sub>, filtered and concentrated to give 0.41 g of white solid. The combined aqueous phase was back extracted with 3:1 chloroform/-isopropanol and this organic phase was separated, dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo to give 1.6 g of white solid. The two crops of solid were combined to give 2.02 g (90%) of the title compound.

**<sup>1</sup>H-NMR**

IS-MS, m/e 235.1 (M+1)

25 **1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-hydroxypiperidine**

To a stirring solution of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.4 g, 7.4 mmol), 1-hydroxybenzotriazole hydrate (1.0 g, 7.4 mmol) and N,N-diisopropylethylamine (1.4 mL) in DMF (20 mL) was added a solution of 1-(D-phenylglycinyl)-4-hydroxypiperidine (2.0 g, 7.38 mmol) in DMF (10 mL) followed by a solution of 4-methoxybenzoic acid (1.0 g, 6.7 mmol) in DMF (10 mL).

After stirring overnight at room temperature, the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic phase was washed again with water followed by saturated aqueous NaHCO<sub>3</sub> (2X) and 5 brine, then dried with MgSO<sub>4</sub>, filtered and concentrated in vacuo to give 2.4 g of off-white solid. A portion of this material (2.0 g) was dissolved in a minimal amount of dichloromethane and chromatographed over silica gel, eluting with a gradient of dichloromethane through 50% ethyl 10 acetate/dichloromethane. The product-containing fractions were combined and concentrated in vacuo to give 1.3 g (60%) of a white foam.

<sup>1</sup>H-NMR

IS-MS, m/e 369.2 (M+1)

15 Analysis for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>:

Calcd: C, 68.46; H, 6.57; N, 7.60;

Found: C, 67.88; H, 6.73; N, 7.33.

Analytical RPHPLC, Method 1, RT = 24.24 min (100%)

20 **1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-oxopiperidine**  
**(Oxidation Method B)** To a stirring solution of oxalyl chloride (0.26 mL, 3 mmol) in dichloromethane (6.5 mL) at -50 °C, was added a solution of DMSO (0.43 mL, 6 mmol) in dichloromethane (1.3 mL). After 3 min, a solution of 25 1-(4-methoxybenzoyl-D-phenylglycanyl)-4-hydroxypiperidine (1.0 g, 2.7 mmol) in dichloromethane (4 mL) was added and the solution was allowed to warm to -20 °C over 45 min. Triethylamine (2 mL) was then added and the solution was allowed to warm to room temperature. The solution was then 30 diluted with dichloromethane and water and the layers were separated. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated in vacuo. The residue

was dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with a gradient of dichloromethane through 50% ethyl acetate/dichloromethane. The product containing fractions were combined and 5 concentrated in vacuo to give 0.77 g (78%) of a white foam.

<sup>1</sup>H-NMR

IS-MS, m/e 367.2 (M+1)

Analysis for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>:

Calcd: C, 68.84; H, 6.05; N, 7.65;

10 Found: C, 68.33; H, 6.01; N, 7.27.

Analytical RPHPLC, Method 1, RT = 25.52 min (100%)

**General Procedure:** Unless otherwise indicated, the product of Examples 292-303 was obtained from 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-oxopiperidine and the indicated amine 15 using the alkylation procedure described for Example 292 (Alkylation Method C).

**Example 292.**

20 **1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(1-pyrrolidinyl)-piperidine**

(**Alkylation Method C**) To a stirring solution of 1-(4-methoxybenzoyl-D-phenylglycinyl)-4-oxopiperidine (50 mg, 0.14 mmol) and pyrrolidine (0.011 mL, 0.13 mmol) in 25 1,2-dichloroethane (1 mL) was added sodium triacetoxyborohydride (45 mg, 0.21 mmol). After stirring overnight, the mixture was loaded onto an SCX column (pretreated with a 5% glacial acetic acid in methanol solution), rinsed with methanol (2 column volumes) and eluted with a 30% 2 N 30 ammonia/methanol in dichloromethane solution. The solution was concentrated in vacuo. The product containing fractions

were combined and concentrated in vacuo to give 48 mg (87%) of the title compound.

1H-NMR

IS-MS, m/e 422.0 (M+1)

5 Analytical RPHPLC, Method 1, RT = 21.02 min (100%)

**Example 293.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(1-piperidinyl)-piperidine**

10 Prepared from piperidine (49%).

1H-NMR

IS-MS, m/e 436.0 (M+1)

Analytical RPHPLC, Method 1, RT = 22.14 min (100%)

15 **Example 294.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-methylpiperidin-1-yl)piperidine**

Prepared from 4-methylpiperidine (78%).

1H-NMR

20 IS-MS, m/e 450.0 (M+1)

Analytical RPHPLC, Method 1, RT = 24.06 min (100%)

**Example 295.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-methylpiperazin-1-yl)piperidine**

Prepared from 1-methylpiperazine (98%).

1H-NMR

IS-MS, m/e 451.0 (M+1)

Analytical RPHPLC, Method 1, RT = 18.66 min (99%)

**Example 296.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-ethylpiperazin-1-yl)piperidine**

Prepared from 1-ethylpiperazine (76%).

5     $^1\text{H-NMR}$

IS-MS, m/e 465.0 (M+1)

Analytical RPHPLC, Method 1, RT = 19.11 min (100%)

**Example 297.**

10    **1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-isopropyl-piperazin-1-yl)piperidine**

Prepared from 1-isopropylpiperazine (83%).

1H-NMR

IS-MS, m/e 479.2 (M+1)

15    Analysis for  $\text{C}_{28}\text{H}_{38}\text{N}_4\text{O}_3 \cdot 0.3\text{H}_2\text{O}$ :

Calcd:    C, 69.48; H, 8.04; N, 11.58;

Found:    C, 69.22; H, 7.91; N, 11.34.

Analytical RPHPLC, Method 1, RT = 19.56 min (99%)

20    **Example 298.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(hexahydro-1,4-diazapin-1-yl)piperidine hydrochloride**

1H-NMR

IS-MS, m/e 451.0 (M+1)

25    Analytical RPHPLC, Method 1, RT = 16.86 min (100%)

**Example 299.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[4-methyl-(hexahydro-1,4-diazapin-1-yl)]piperidine**

30    Prepared from 4-methyl-hexahydro-1,4-diazapine (63%).

1H-NMR

IS-MS, m/e 465.0 (M+1)

Analytical RPHPLC, Method 1, RT = 18.86 min (98%)

**Example 300.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(3-pyridylamino)-5-piperidine**

Prepared from 3-aminopyridine (25%).

<sup>1</sup>H-NMR

IS-MS, m/e 445.0 (M+1)

Analytical RPHPLC, Method 1, RT = 23.87 min (100%)

10

**Example 301.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[ (N-methyl-N-benzyl)amino]piperidine**

Prepared from N-methylbenzylamine (89%).

15 <sup>1</sup>H-NMR

IS-MS, m/e 472.0 (M+1)

Analysis for C<sub>29</sub>H<sub>33</sub>N<sub>3</sub>O<sub>3</sub> · 0.1H<sub>2</sub>O:

Calcd: C, 73.58; H, 7.07; N, 8.88;

Found: C, 73.39; H, 7.19; N, 9.06.

20 Analytical RPHPLC, Method 1, RT = 26.27 min (98%)

**Example 302.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-[ (3-pyridylmethyl)amino]piperidine**

25 Prepared from 3-aminomethylpyridine (72%).

<sup>1</sup>H-NMR

IS-MS, m/e 459.0 (M+1)

Analysis for C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub> · 0.2H<sub>2</sub>O:

Calcd: C, 70.17; H, 6.63; N, 12.12;

30 Found: C, 70.00; H, 6.53; N, 12.13.

Analytical RPHPLC, Method 1, RT = 16.38 min (100%)

**Example 303.****1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-[(4-pyridylmethyl)-amino]piperidine**

prepared from 4-aminomethylpyridine (46%).

5    <sup>1</sup>H-NMR

IS-MS, m/e 459.0 (M+1)

Analysis for C<sub>27</sub>H<sub>30</sub>N<sub>4</sub>O<sub>3</sub>·0.9H<sub>2</sub>O:

Calcd:    C, 68.30; H, 6.75; N, 11.80;

Found:    C, 67.99; H, 6.42; N, 11.59.

10    Analytical RPHPLC, Method 1, RT = 18.36 min (100%)

**Examples 304 to 314**

**General Procedure:** Unless otherwise indicated, the product of Examples 304-314 was obtained from 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine and the indicated aldehyde or ketone using the alkylation procedure described for Example 304 (Alkylation Method D).

**Example 304.**

20    **1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(2-pyridylmethyl)-piperazine**

**(Alkylation Method D)** To a stirring solution of 1-(4-methoxybenzoyl-D-phenylglycinyl)piperazine (50 mg, 0.14 mmol) and 2-pyridinecarboxaldehyde (0.020 mL, 23 mg, 0.21 mmol) in 5% acetic acid/methanol (1 mL) was added NaBH<sub>3</sub>CN (20 mg, 0.32 mmol). After 4 h, the solution was loaded onto an SCX column (pretreated with a 5% glacial acetic acid in methanol solution), rinsed with methanol (2 column volumes) and eluted with a 30% 2N ammonia/methanol in dichloromethane solution. The solution was concentrated in vacuo and the residue was dissolved in a minimum amount of dichloromethane and chromatographed over silica gel, eluting with

dichloromethane, followed by 50% ethyl acetate/dichloromethane, and finally with a gradient of 2%-10% (2 N NH<sub>3</sub> in MeOH) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 30 mg (48%) of the title compound.

1H-NMR

IS-MS, m/e 444.9 (M+1)

Analytical RPHPLC, Method 1, RT = 21.70 min (100%)

10 **Example 305.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(3-pyridylmethyl)-piperazine**

Prepared from 3-pyridine carboxaldehyde (42%).

1H-NMR

15 IS-MS, m/e 444.9 (M+1)

Analytical RPHPLC, Method 1, RT = 17.84 min (99%)

**Example 306.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(4-pyridylmethyl)-piperazine**

Prepared from 4-pyridine carboxaldehyde (45%).

1H-NMR

IS-MS, m/e 444.9 (M+1)

Analytical RPHPLC, Method 1, RT = 18.36 min (99%)

25

**Example 307.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-phenethylpiperazine**

Prepared from phenylacetaldehyde (34%).

1H-NMR

30 IS-MS, m/e 458.0 (M+1)

Analytical RPHPLC, Method 1, RT = 27.44 min (100%)

**Example 308.****1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(3-pentyl)piperazine**

Prepared from 3-pantanone (88%).

1H-NMR

5 IS-MS, m/e 424.0 (M+1)

Analytical RPHPLC, Method 1, RT = 23.62 min (100%)

**Example 309.****1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-cyclopentyl-**10 **piperazine**

Prepared from cyclopantanone (95%).

1H-NMR

IS-MS, m/e 422.0 (M+1)

Analytical RPHPLC, Method 1, RT = 20.76 min (100%)

15

**Example 310.****1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(4-methyl-cyclohexyl)piperazine**

Prepared from 4-methylcyclohexanone (46%).

20 1H-NMR

IS-MS, m/e 450.0 (M+1)

Analytical RPHPLC, Method 1, RT = 27.07 min (isomer 1),  
27.74 min (isomer 2).25 **Example 311.****1-(4-Methoxybenzoyl-D-phenylglycinyl)-4-(tetrahydro-thiopyran-4-yl)piperazine**

Prepared from tetrahydro-4H-thiopyran-4-one (86%).

1H-NMR

30 IS-MS, m/e 453.9 (M+1)

Analytical RPHPLC, Method 1, RT = 22.96 min (100%)

**Example 312.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(2-indanyl)-piperazine**

Prepared from 2-indanone (92%).

5     $^1\text{H-NMR}$

IS-MS, m/e 469.9 (M+1)

Analytical RPHPLC, Method 1, RT = 26.32 min (100%)

**Example 313.**

10    **1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-benzylpiperazine**

Prepared from benzaldehyde (87%).

1H-NMR

IS-MS, m/e 444.0 (M+1)

Analytical RPHPLC, Method 1, RT = 25.78 min (96%)

15

**Example 314.**

**1-(4-Methoxybenzoyl-D-phenylglycanyl)-4-(cyclohexylmethyl)piperazine**

Prepared from cyclohexanecarboxaldehyde (86%).

20     $^1\text{H-NMR}$

IS-MS, m/e 450.2 (M+1)

Analytical RPHPLC, Method 1, RT = 28.07 min (94%)

**Examples 315 to 316**

25    **Preparation of Starting Materials**

**1-(Boc-D-Phenylglycanyl)-4-oxopiperidine**

Using Oxidation Method B, the title compound was prepared from 1-(Boc-D-phenylglycanyl)-4-hydroxypiperidine (44%).

30     $^1\text{H-NMR}$

IS-MS, m/e 333.0 (M+1)

**1-(Boc-D-Phenylglycanyl)-4-(4-methylpiperazin-1-yl)-piperidine**

Using Alkylation Method C, the title compound was prepared from 1-(Boc-D-phenylglycanyl)-4-oxopiperidine and 5 methylpiperazine (65%).

**<sup>1</sup>H-NMR**

IS-MS, m/e 417.3 (M+1)

Analysis for C<sub>23</sub>H<sub>36</sub>N<sub>4</sub>O<sub>3</sub>:

Calcd: C, 66.32; H, 8.71; N, 13.45;

10 Found: C, 66.25; H, 8.58; N, 13.42.

**1-D-Phenylglycanyl-4-(4-methylpiperazin-1-yl)piperidine**

HCl gas was bubbled through a stirring solution of 1-(Boc-D-phenylglycanyl)-4-(4-methylpiperazin-1-yl)piperidine (1.36 g, 3.26 mmol) in ethyl acetate (150 mL). A white precipitate was formed immediately, but then went back into solution. After about 5 min, a white precipitate again fell out of solution. After 10 min, the addition of HCl was discontinued and after stirring for a total of 1 h, the 20 mixture was filtered to give 1.38 g (quantitative) of white solid.

**<sup>1</sup>H-NMR**

IS-MS, m/e 317.3 (M+1)

Analysis for C<sub>18</sub>H<sub>28</sub>N<sub>4</sub>O·2.9HCl·2.5H<sub>2</sub>O:

25 Calcd: C, 46.27; H, 7.74; N, 11.99; Cl, 22.01;

Found: C, 46.06; H, 7.51; N, 11.63; Cl, 21.78.

**General Procedure:** The product of Examples 315-316 was prepared from 1-(D-phenylglycanyl)-4-(4-methylpiperazin-30 1-yl)piperidine and the indicated acid using Coupling Method B.

**Example 315.**

**1-(Indole-6-carbonyl-D-phenylglycanyl)-4-(4-methylpiperazin-1-yl)piperidine**

Prepared from indole-6-carboxylic acid (66%).

5     $^1\text{H-NMR}$

IS-MS, m/e 460.2 (M+1)

Analytical RPHPLC, Method 1, RT = 17.83 min (99%)

**Example 316.**

10    **1-(3-Chloroindole-6-carbonyl-D-phenylglycanyl)-4-(4-methylpiperazinyl)piperidine**

Prepared from 3-chloroindole-6-carboxylic acid (69%).

1H-NMR

IS-MS, m/e 494.3 (M+1)

15    Analytical RPHPLC, Method 1, RT = 22.99 min (99%)

**Examples 317 to 320****Preparation of Starting Materials**

20    **(Cbz-D-phenylglycanyl)piperazine.**

Using Deprotection Method D, the title compound was prepared from 1-(Cbz-D-phenylglycanyl)-4-Boc-piperazine (85%)

1H-NMR

IS-MS, m/e 354.2 (M+1)

25    Analysis for  $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_3 \cdot 0.2\text{H}_2\text{O}$ :

Calcd:    C, 67.28; H, 6.61; N, 11.77;

Found:    C, 67.10; H, 6.46; N, 11.63.

30    **1-(Cbz-D-phenylglycanyl)-4-(1-methylpiperidin-4-yl)-piperazine**

Using Alkylation Method C, the title compound was prepared from (Cbz-D-phenylglycanyl)piperazine and 1-methylpiperidin-

4-one (49%). The product was purified using silica gel chromatography, eluting with a gradient of dichloromethane through 10% (2 N ammonia in methanol) / dichloromethane.

1H-NMR

5 IS-MS, m/e 451.3 (M+1)

Analysis for C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>:

Calcd: C, 69.31; H, 7.61; N, 12.43;

Found: C, 69.36; H, 7.71; N, 13.14.

10 **1-D-Phenylglycinyl-4-(1-methylpiperidin-4-yl)piperazine dihydrochloride.**

To a stirring suspension of 5% Pd/C (0.6 g) in ethanol (25 mL) under nitrogen was added a solution of 1-(Cbz-D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine (2.6 g, 5.77 mmol) and acetic acid (1.6 mL) in ethanol (50 mL). The flask was placed under vacuum and the atmosphere was replaced with hydrogen (balloon). After 4 h, diatomaceous earth was added and the mixture was filtered through a pad of diatomaceous earth and concentrated in vacuo. The residue was dissolved in ethyl acetate and HCl gas was bubbled through the stirring solution to precipitate the dihydrochloride salt. The mixture was filtered and the solid was dried in vacuo to give 2.6 g (quantitative) of the title compound.

25 1H-NMR

IS-MS, m/e 317.3 (M+1)

**General Procedure:** The product of Examples 317-320 was prepared from 1-(D-phenylglycinyl)-4-(1-methylpiperidin-4-yl)piperazine dihydrochloride and the indicated acid using Coupling Method B.

**Example 317.**

**1- (4-Methoxybenzoyl-D-phenylglycinyl) -4- (1-methylpiperidin-4-yl)piperazine**

Prepared from 4-methoxybenzoic acid (19%).

5     $^1\text{H-NMR}$

IS-MS, m/e 451.0 (M+1)

Analytical RPHPLC, Method 1, RT = 16.76 min (100%)

**Example 318.**

10    **1- (Indole-6-carbonyl-D-phenylglycinyl) -4- (1-methylpiperidin-4-yl)piperazine**

Prepared from indole-6-carboxylic acid (65%).

1H-NMR

IS-MS, m/e 460.2 (M+1)

15    Analytical RPHPLC, Method 1, RT = 16.68 min (100%)

**Example 319.**

**1- (3-Methylindole-6-carbonyl-D-phenylglycinyl) -4- (1-methylpiperidin-4-yl)piperazine**

20    Prepared from 3-methylindole-6-carboxylic acid (50%).

1H-NMR

IS-MS, m/e 474.3 (M+1)

Analytical RPHPLC, Method 1, RT = 22.20 min (98%)

25    **Example 320.**

**1- (3-Chloroindole-6-carbonyl-D-phenylglycinyl) -4- (1-methylpiperidin-4-yl)piperazine**

Prepared from 3-chloroindole-6-carboxylic acid (76%).

1H-NMR

30    IS-MS, m/e 493.9 (M+1)

Analytical RPHPLC, Method 1, RT = 22.66 min (100%)

**Examples 321 to 324****Preparation of Starting Materials****Ethyl hydroxyimino-pyridine-2-acetate**

5 To a stirring solution of ethyl pyridine-2-acetate (12.6 g, 76.3 mmol) in acetic acid (19 mL) at 5 °C was added a solution of sodium nitrite (6.05 g, 87.7 mmol) in water (12 mL) at a rate sufficient to maintain the internal temperature below 15 °C. After complete addition and an additional 30 min, an additional 30 mL of water was added. The resulting white precipitate was filtered, washed with water, saturated aqueous NaHCO<sub>3</sub>, and again with water. The solid was then dried under vacuum to give 14.1 g (95%) of the title compound.

15 <sup>1</sup>H-NMR

IS-MS, m/e 194.9 (M+1)

Analysis for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>:

Calcd: C, 55.67; H, 5.19; N, 14.43;

Found: C, 55.79; H, 5.14; N, 14.13.

20

**Boc-D,L-(2-Pyridinyl)glycine ethyl ester**

To a solution of ethyl hydroxyimino-pyridine-2-acetate (7.8 g, 40.15 g) in ethanol (175 mL) and glacial acetic acid (20 mL) was added 5% Pd/C, and the mixture was shaken in a hydrogenation apparatus under an atmosphere of hydrogen at 3.1 bar for 4 h. The mixture was filtered through diatomaceous earth and concentrated in vacuo. The residue was dissolved in THF/H<sub>2</sub>O (1:1, 240 mL) and treated with di-tert-butyl dicarbonate (14.23 g, 65.2 mmol) and sodium bicarbonate (27.4 g, 326 mmol). After stirring at room temperature for 2 h, the solution was concentrated in vacuo and the residue was partitioned between EtOAc and water.

The organic phase was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified via chromatography over silica gel, eluting with a stepwise gradient of 10-20% ethyl acetate in dichloromethane, to give 8.11 g (72%) of a yellow oil.

1H-NMR

IS-MS, m/e 281.1 (M+1)

10 **1-[Boc-D,L-(2-Pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine**

To a stirring solution of Boc-D,L-(2-pyridinyl)glycine ethyl ester (3.89 g, 13.88 mmol) in 1, 4-dioxane (20 mL) was added a solution of lithium hydroxide hydrate (0.64 g, 15.27 mmol) in water (20 mL). After stirring for 2 h, the solution was concentrated in vacuo. The residue was dried under vacuum for 15 h then dissolved in DMF (50 mL). The solution was cooled to 0 °C, purged with nitrogen, and diethyl cyanophosphonate (2.5 g, 16.66 mmol) was slowly added.

20 After 2 min, the solution was treated with a solution of 1-methyl-4,4'-bispiperidine dihydrochloride (3.9 g, 15.27 mmol) and triethylamine (6.8 mL, 48.58 mmol) in DMF (50 mL).

After 2 h, the cold bath was removed and the solution was allowed to stir overnight. The next morning, the solvent was 25 evaporated in vacuo and the resulting oil was partitioned between 3:1 chloroform:isopropyl alcohol and saturated aqueous sodium bicarbonate. The organic phase was dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was purified via chromatography over silica gel, eluting with a stepwise gradient of 5-9% (2 N ammonia in methanol) in dichloromethane to give 2.6 g (45%) of a clear oil.

1H-NMR

IS-MS, m/e 417.2 (M+1)

**1-[D,L-(2-Pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine**

5   **(Deprotection Method E)** To a stirring solution of 1-[Boc-D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine (1.8 g, 4.32 mmol) in dichloromethane (90 mL) was added anisole (2.3 mL, 21.6 mmol), followed by trifluoroacetic acid ( 8.3 mL, 108 mmol). After 4 h, the solvents were evaporated in  
10 vacuo, the crude product was dissolved in methanol and loaded onto an SCX column (pretreated with a 5% glacial acetic acid in methanol solution), rinsed with methanol (2 column volumes) and eluted with a 30% 2 N ammonia/methanol in dichloromethane solution. The product containing  
15 fractions were combined and concentrated in vacuo to give 1.08 g (77%) of a yellow oil.

1H-NMR

IS-MS, m/e 317.2 (M+1)

Analysis for C<sub>18</sub>H<sub>28</sub>N<sub>4</sub>O·0.55H<sub>2</sub>O:

20   Calcd:   C, 66.25; H, 8.99; N, 17.17;  
Found:    C, 66.07; H, 8.49; N, 16.66.

General Procedure: The product of Examples 321-324 was prepared from 1-[D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine and the indicated acid using the procedure described for Example 321 (Coupling Method D).

**Example 321.**

1-[Indole-6-carbonyl-D,L-(2-pyridinyl)glycanyl]-1'-methyl-  
30 4,4'-bispiperidine  
**(Coupling Method D)** To a stirring solution of 1-[D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine (0.3 g,

0.95 mmol) in N, N-dimethylformamide (3 mL) was added indole-6-carboxylic acid (0.15 g, 0.95 mmol) and 1-hydroxybenzotriazole hydrate (0.13 g, 0.95 mmol), followed by 1,3-dicyclohexylcarbodiimide (0.19 g, 0.95 mmol). After 5 stirring overnight, the mixture was filtered and the filtrate was loaded onto an SCX column (pretreated with a 5% glacial acetic acid in methanol solution), rinsed with methanol (2 column volumes) and eluted with a 30% (2 N ammonia in methanol) in dichloromethane solution. The 10 product containing fractions were concentrated in vacuo and the residue was chromatographed over silica gel, eluting with a stepwise gradient of 5-9% (2 N ammonia in methanol) in dichloromethane to give 255 mg (58%) of a tan foam.

1H-NMR

15 IS-MS, m/e 460.3 (M+1)

Analytical RPHPLC, Method 1, RT = 14.90 min (100%)

**Example 322.**

**1-[4-Methoxybenzoyl-D,L-(2-pyridinyl)glycinyl]-1'-methyl-  
20 4,4'-bis(piperidine)**

Prepared from 4-methoxybenzoic acid (53%).

1H-NMR

IS-MS, m/e 451.2 (M+1)

Analytical RPHPLC, Method 1, RT = 14.79 min (98%)

25

**Example 323.**

**1-[3-Methylindol-6-carbonyl-D,L-(2-pyridinyl)glycinyl]-1'-  
methyl-4,4'-bis(piperidine)**

Prepared from 3-methyl-6-carboxyindole (40%).

30 1H-NMR

IS-MS, m/e 474.3 (M+1)

Analytical RPHPLC, Method 1, RT = 18.28 min (97%)

**Example 324.**

**1-[3-Chloroindole-6-carbonyl-D,L-(2-pyridinyl)glyciny]-1'-methyl-4,4'-bis(piperidine)**

5 Prepared from 3-chloro-6-carboxyindole (71%).

1H-NMR

IS-MS, m/e 494.0 (M+1)

Analysis for C<sub>27</sub>H<sub>32</sub>N<sub>5</sub>O<sub>2</sub>Cl·0.2H<sub>2</sub>O:

Calcd: C, 65.17; H, 6.56; N, 14.07;

10 Found: C, 65.57; H, 6.56; N, 13.23.

Analytical RPHPLC, Method 1, RT = 20.96 min (99%)

**Examples 325 to 328****Preparation of Starting Materials**

15

**Ethyl hydroxyimino-pyridine-3-acetate**

Using the procedure of Tikk et al. [Acta. Chimica Hungarica, 114(3-4), 355], a mixture of ethyl hydroxyimino-pyridine-3-acetate and n-butyl hydroxyimino-pyridine-3-acetate was prepared from ethyl pyridine-3-acetate and n-butyl nitrite.

1H-NMR

IS-MS, m/e 195 (M+1), 223.1 (M+1)

**Boc-D,L-(3-Pyridinyl)glycine ethyl ester**

25 Using methods substantially equivalent to those described above in preparation of Boc-D,L-(2-pyridinyl)glycine ethyl ester, the title compound was prepared from the above ethyl hydroxyimino-pyridine-3-acetate (57%).

1H-NMR

30 IS-MS, m/e 281.1 (M+1)

**1-[Boc-D,L-(3-Pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine)**

Using methods substantially equivalent to those described in preparation of 1-[Boc-D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine), the title compound was prepared from Boc-D,L-(3-pyridinyl)glycine ethyl ester (20%).

<sup>1</sup>H-NMR

IS-MS, m/e 417.2 (M+1)

**10 1-[D,L-(3-Pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine)**

Using methods substantially equivalent to those described in preparation of 1-[D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine), the title compound was prepared from 1-[Boc-D,L-(3-pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine) (75%).

<sup>1</sup>H-NMR

IS-MS, m/e 317.2 (M+1)

**General Procedure:** The product of Examples 325-328 was prepared from 1-[D,L-(3-pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine) and the indicated acid using the procedure described for Example 325 (Coupling Method D).

**Example 325.**

**25 1-[4-Methoxybenzoyl-D,L-(3-pyridinyl)glycanyl]-1'-methyl-4,4'-bis(piperidine)**

Prepared from 4-methoxybenzoic acid (45%).

<sup>1</sup>H-NMR

IS-MS, m/e 451.2 (M+1)

**30 Analysis for C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>·1.2H<sub>2</sub>O:**

Calcd: C, 66.13; H, 7.77; N, 11.87;

Found: C, 66.61; H, 7.27; N, 11.87.

Analytical RPHPLC, Method 1, RT = 12.98 min (98%)

**Example 326.**

**1-[Indole-6-carbonyl-D,L-(3-pyridinyl)glyciny1]-1'-methyl-**

**5 4,4'-bis(piperidine)**

Prepared from indole-6-carboxylic acid (36%).

1H-NMR

IS-MS, m/e 460.3 (M+1)

Analysis for C<sub>27</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>·1.5H<sub>2</sub>O:

10 Calcd: C, 66.64; H, 7.46; N, 14.39;

Found: C, 66.71; H, 6.87; N, 13.89.

Analytical RPHPLC, Method 1, RT = 14.39 min (100%)

**Example 327.**

**1-[3-Methylindole-6-carbonyl-D,L-(3-pyridinyl)glyciny1]-1'-**

**methyl-4,4'-bis(piperidine)**

Prepared from 3-methylindole-6-carboxylic acid (40%).

1H-NMR

IS-MS, m/e 474.3 (M+1)

20 Analysis for C<sub>28</sub>H<sub>35</sub>N<sub>5</sub>O<sub>2</sub>·1.6H<sub>2</sub>O:

Calcd: C, 66.93; H, 7.66; N, 13.94;

Found: C, 66.63; H, 6.99; N, 13.52.

Analytical RPHPLC, Method 1, RT = 16.98 min (98%)

25 **Example 328.**

**1-[3-Chloroindole-6-carbonyl-D,L-(3-pyridinyl)glyciny1]-1'-**

**methyl-4,4'-bis(piperidine)**

Prepared from 3-chloroindole-6-carboxylic acid (46%).

1H-NMR

30 IS-MS, m/e 494.2 (M+1)

Analysis for C<sub>27</sub>H<sub>32</sub>ClN<sub>5</sub>O<sub>2</sub>·1.1H<sub>2</sub>O:

Calcd: C, 63.11; H, 6.71; N, 13.63;

Found: C, 62.84; H, 6.32; N, 13.26.

Analytical RP-HPLC, Method 1, RT = 19.63 min (100%)

**Examples 329 to 330**

**5 Preparation of Starting Materials**

**Boc-D-[3-(ethanesulfonylamino)phenyl]glycine**

To a stirring solution of D-3-(ethanesulfonylamino)-phenylglycine (20 g, 77.43 mmol) and sodium carbonate

10 (8.2 g, 77.43 mmol) in 3:1 THF/water (200 mL) at 0 °C, was added di-tert-butyl dicarbonate (18.5 g, 85.17 mmol). After stirring for 30 min, the cold bath was removed; and after an additional 30 min at room temperature, the solvent was removed and the residue was partitioned between ethyl acetate and water. The aqueous layer was acidified to pH 2 with KHSO<sub>4</sub> and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried with Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give 17.51 g (63%) of a white solid.

20 <sup>1</sup>H-NMR

IS-MS, m/e 357.0 (M-1)

**1-[Boc-D-[3-(ethanesulfonylamino)phenyl]glycyl]-1'-methyl-4,4'-bis(piperidine)**

25 To a stirring solution of Boc-D-[3-(ethanesulfonylamino)-phenyl]glycine (5 g, 13.95 mmol) in dichloromethane at 0 °C, diethyl cyanophosphonate (2.12 mL, 13.95 mmol) and diisopropylethylamine (4.86 mL, 27.91 mmol) and then

N-methylbis(piperidine) dihydrobromide (4.32 g, 12.56 mmol) 30 were added; and the mixture was stirred at 0 °C for 3 h. The reaction mixture was then stirred at room temperature overnight, filtered, washed with saturated aqueous sodium

bicarbonate and water, dried over sodium sulfate, filtered and concentrated in vacuo to give 5 g (76%) of a tan foam.

<sup>1</sup>H-NMR

IS-MS, m/e (M+1)

5

**1-[D-[3-(Ethanesulfonylamino)phenyl]glycanyl]-1'-methyl-4,4'-bis(piperidine)**

Using Deprotection Method E, the title compound was prepared from 1-[Boc-D-[3-(ethanesulfonylamino)phenyl]glycanyl]-1'-methyl-4,4'-bis(piperidine) (74%).

<sup>1</sup>H-NMR

IS-MS, m/e 423.1(M+1)

Analysis for C<sub>21</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>S·1.3H<sub>2</sub>O:

Calcd: C, 56.55; H, 8.27; N, 12.56;

15 Found: C, 56.68; H, 7.87; N, 11.97.

**General Procedure:** The product of Examples 329-330 was prepared from 1-[D-[3-(ethanesulfonylamino)phenyl]glycanyl]-1'-methyl-4,4'-bis(piperidine) and the indicated acid using 20 the procedure described for Example 321 (Coupling Method D).

**Example 329.**

**1-[4-Methoxybenzoyl-D-[3-(ethanesulfonylamino)-phenyl]glycanyl]-1'-methyl-4,4'-bis(piperidine)**

25 Prepared from 4-methoxybenzoic acid (43%).

<sup>1</sup>H-NMR

IS-MS, m/e 557.3(M+1)

Analysis for C<sub>29</sub>H<sub>40</sub>N<sub>4</sub>O<sub>5</sub>S·0.9H<sub>2</sub>O:

Calcd: C, 60.79; H, 7.35; N, 9.78;

30 Found: C, 60.49; H, 7.08; N, 9.62.

Analytical RPHPLC, Method 1, RT = 22.68 min (98%)

**Example 330.**

**1-[Indole-6-carbonyl-D-[3-(ethanesulfonylamino)-phenyl]glycanyl]-1'-methyl-4,4'-bispiperidine**

Prepared from indole-6-carboxylic acid (58%).

5       $^1\text{H-NMR}$

IS-MS, m/e (M+1)

Analysis for  $\text{C}_{30}\text{H}_{39}\text{N}_5\text{O}_4\text{S} \cdot 2\text{H}_2\text{O}$ :

Calcd:    C, 59.88; H, 7.20; N, 11.64;

Found:    C, 59.97; H, 6.65; N, 11.43.

10     Analytical RPHPLC, Method 1, RT = 29.02 min (98%)

**Example 331.**

**1-(3-Aminoindazole-5-carbonyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine**

15    To a stirring solution of 1-(3-cyano-4-fluorobenzoyl-D-phenylglycanyl)-1'-methyl-4,4'-bispiperidine (120 mg, 0.259 mmol) in p-dioxane (6 mL) was added hydrazine hydrate (26 mg, 0.518 mmol), and the solution was heated to reflux.

After 2 h, the heat was removed and the solvent was

20    evaporated in vacuo. The residue was dissolved in ethanol and heated to reflux. After 12 h, the solution was cooled and concentrated in vacuo. The residue was chromatographed over silica gel, eluting with 10% (2 N ammonia in methanol) in dichloromethane. The product containing fractions were 25    combined and concentrated in vacuo to give 75 mg (62%) of an off white solid.

$^1\text{H-NMR}$

IS-MS, m/e 475.3 (M+1)

Analytical RPHPLC, Method 1, RT = 14.72 min (100%)

**Example 332.****1-(1-Methyl-3-aminoindazole-5-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine**

Using methods substantially equivalent to those described in Example 331, the title compound was prepared from methylhydrazine and 1-(3-cyano-4-fluorobenzoyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine (31%).

<sup>1</sup>H-NMR

ES-MS, m/e 489.2 (M+1)

Analytical RPHPLC [Vydac C18, linear gradient of 98/2 - 80/20 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min] RT = 38.99 min (100%).

**Example 333.****1-(Imidazo[1,2-a]pyrimidine-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bispiperidine****Imidazo[1,2-a]pyrimidine-2-carboxylic acid**

To a stirring solution of ethyl 1-(imidazo[1,2-a]pyrimidine-2-carboxylate (1 g, 5.2 mmol) [Abignente, et al. Eur. J. Med. Chem. (1994) 29, 279] in ethanol (30 mL) was added 2 N aqueous KOH (10 mL, 20 mmol). The solution was heated to reflux; and after 2 h, the heating mantle was removed, the solution was allowed to cool and the solvent was removed by rotary evaporation. The residue was dissolved in water (20 mL) and acidified to pH 3 with 5 N HCl. The resulting precipitate was filtered, washed with water and dried in vacuo to give 700 mg (83%) of a tan solid.

<sup>1</sup>H-NMR

FD-MS, m/e 163.2 (M+1)

Analysis for C<sub>7</sub>H<sub>5</sub>N<sub>3</sub>O<sub>2</sub>:

Calcd: C, 51.54; H, 3.09; N, 25.76;

Found: C, 51.12; H, 3.25; N, 25.25.

**1-(Imidazo[1,2-a]pyrimidine-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

5 Using Coupling Method B, the title compound was prepared from imidazo[1,2-a]pyrimidine-2-carboxylic acid and 1-D-phenylglycinyl-1'-methyl-4,4'-bis(piperidine) (56%).

**<sup>1</sup>H-NMR**

IS-MS, m/e 461.2 (M+1)

10 Analytical RPHPLC [Vydac C18, linear gradient of 98/2 - 80/20 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min] RT = 32.72 min (96%).

**Example 334.**

15 **1-(5,6,7,8-Tetrahydro-imidazo[1,2-a]pyrimidine-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine)**

To a stirring solution of 1-(imidazo[1,2-a]pyrimidine-2-carbonyl-D-phenylglycinyl)-1'-methyl-4,4'-bis(piperidine) (250 mg, 0.542 mmol) in ethanol (5 mL) was added sodium borohydride (103 mg, 2.71 mmol). After 24 h, the mixture was diluted with water and extracted 3 times with dichloromethane. The organic phase was dried ( $MgSO_4$ ), filtered and concentrated in vacuo. The residue was dissolved in dichloromethane and chromatographed over silica gel, eluting with 5% through 10% (2 N  $NH_3$  in MeOH) in dichloromethane. The product containing fractions were combined and concentrated in vacuo to give 55 mg (20%) of the title compound.

**<sup>1</sup>H-NMR**

30 IS-MS, m/e 465.2 (M+1)

Analytical RPHPLC [Vydac C18, linear gradient of 98/2 - 80/20 (0.1% TFA in water / 0.1% TFA in acetonitrile) over 40 min, 1 mL/min] RT = 28.44 min (97%).

5   **Examples 335 to 338**

**Preparation of Starting Materials**

**Ethyl hydroxyimino-pyridine-4-acetate**

The oxime was prepared in 82% yield from ethyl pyridine-4-acetate using a procedure similar to that described above under Examples 321-324 for the preparation of ethyl hydroxyimino-pyridine-2-acetate.

1H-NMR (DMSO)

IS-MS, m/e 194.9 (M+1)

15

**Boc-D,L-(4-Pyridinyl)glycine ethyl ester**

The protected amino ester is prepared from ethyl hydroxyimino-pyridine-4-acetate using a procedure similar to that described above under Examples 321-324 for the preparation of Boc-D,L-(2-pyridinyl)glycine ethyl ester.

**1-[Boc-D,L-(4-Pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine**

The protected amide is prepared from Boc-D,L-(4-pyridinyl)-glycine ethyl ester and 1-methyl-4,4'-bispiperidine dihydrochloride using a procedure similar to that described above under Examples 321-324 for the preparation of 1-[Boc-D,L-(2-pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine.

30   **1-[D,L-(4-Pyridinyl)glycanyl]-1'-methyl-4,4'-bispiperidine**

The amine is prepared from 1-[Boc-D,L-(4-pyridinyl)-glycanyl]-1'-methyl-4,4'-bispiperidine using a procedure

similar to that described above under Examples 321-324 for the preparation of 1-[D,L-(2-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine.

5   **General Procedure:** The product of Examples 335-338 is prepared from 1-[D,L-(4-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine and the indicated acid using Coupling Method D.

10   **Example 335.**

**1-[4-Methoxybenzoyl-D,L-(4-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine**

From 4-methoxybenzoic acid.

15   **Example 336.**

**1-(Indole-6-carbonyl-D,L-(4-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine**

From indole-6-carboxylic acid.

20   **Example 337.**

**1-[3-Methylindole-6-carbonyl-D,L-(4-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine**

From 3-methylindole-6-carboxylic acid.

25   **Example 338.**

**1-[3-Chloroindole-6-carbonyl-D,L-(4-pyridinyl)glycinyl]-1'-methyl-4,4'-bispiperidine**

From 3-chloroindole-6-carboxylic acid.

30   **Assay protocols**

Enzyme Inhibition assays:

The ability of a test compound to inhibit factor Xa may be evaluated in one or more of the following Enzyme Inhibition assays, or in other standard assays known to those skilled  
5 in the art.

#### Enzyme Inhibition Assay 1

Enzyme assays were carried out at room temperature in 0.1M  
10 phosphate buffer, pH7.4 according to the method of  
Tapparelli et al (J. Biol. Chem. 1993, 268, 4734-4741).  
Purified human factor Xa, trypsin, thrombin and plasmin were  
purchased from Alexis Corporation, Nottingham, UK. Urokinase  
was purchased from Calbiochem, Nottingham, UK. Chromogenic  
15 substrates for these enzymes; pefachrome-FXA, pefachrome-  
TRY, pefachrome-TH, pefachrome-PL and pefachrome-UK were  
purchased from Pentapharm AG, Basel, Switzerland. Product  
(*p*-nitroaniline) was quantified by adsorption at 405nm in 96  
well microplates using a Dynatech MR5000 reader (Dynex Ltd,  
20 Billingshurst, UK). Km and Ki were calculated using SAS PROC  
NLIN (SAS Institute, Cary, NC, USA, Release 6.11) Km values  
were determined as 100.9μM for factor Xa/pefachrome-FXA and  
81.6μM for trypsin/pefachrome-TRY. Inhibitor stock solutions  
were prepared at 40mM in Me2SO and tested at 500μM, 50μM and  
25 5μM. Accuracy of Ki measurements was confirmed by  
comparison with Ki values of known inhibitors of factor Xa  
and trypsin.

In agreement with published data, benzamidine inhibited  
30 factor Xa, trypsin, thrombin, plasmin and urokinase with Ki  
values of 155μM, 21μM, 330nM, 200nM and 100nM respectively.  
NAPAP inhibited thrombin with a Ki value of 3nM. Compounds

of the invention were found to have activity in these assays.

#### Enzyme Inhibition Assay 2

5

Human factor Xa and human thrombin were purchased from Enzyme Research Laboratories (South Bend, Indiana, USA). Other proteases were from other commercial sources. Chromogenic para-nitroanilide peptide protease substrates 10 were purchased from Midwest Biotech (Fishers, Indiana, USA).

The binding affinities for human factor Xa were measured as apparent association constants (Kass) derived from protease 15 inhibition kinetics as described previously.<sup>a,b,c,d</sup> The apparent Kass values were obtained using automated (BioMek-1000) dilutions of inhibitors (Kass determinations are performed in triplicate at each of four-eight inhibitor concentrations) into 96-well plates and chromogenic substrate hydrolysis rates determined at 405 nm using a 20 Thermomax plate reader from Molecular Devices (San Francisco). For factor Xa inhibition, the assay protocol was: 50 µl buffer (0.06 M tris, 0.3 M NaCl, pH 7.4); 25 µl inhibitor test solution (in MeOH); 25 µl human factor Xa (32 nM in 0.03 M tris, 0.15 M NaCl, 1 mg/ml HSA); finally, 150 µl BzIleGluGlyArgpNA (0.3 mM in water) added within 2 min to start hydrolysis. Final factor Xa was 3.2 nM. Free [Xa] and bound [Xa] were determined from linear standard curves 25 on the same plate by use of SoftmaxPro software for each inhibitor concentration and apparent Kass calculated for 30 each inhibitor concentration which produced hydrolysis inhibition between 20% and 80% of the control (3.2 nM factor

Xa): apparent Kass =  $[E:I] / [E_f][I_f] = [E_b] / [E_f][I^o - I_b]$ . The apparent Kass values so obtained are approximately the inverse of the Ki for the respective inhibitors [ $1/appKass = app\ Ki$ ]. The variability of mean apparent Kass values 5 determined at the single substrate concentration was +/- 15%. The assay system Km was measured as  $0.347 \pm 0.031$  mM [n=4]; and Vmax was  $13.11 \pm 0.76$   $\mu\text{M}/\text{min}$ .

Kass values were determined with thrombin and other 10 proteases using the same protocol with the following enzyme and substrate concentrations: thrombin 5.9 nM with 0.2 mM BzPheValArgpNA; XIA 1.2 nM with 0.4 mM pyroGluProArgpNA; XIIa 10 nM with 0.2 mM HDProPheArgpNA; plasmin 3.4 nM with 15 0.5 mM HDValLeuLyspNA; nt-PA 1.2 nM with 0.8 mM HDIleProArgpNA; and urokinase 0.4 nM with 0.4 mM pyroGluGlyArgpNA; aPC 3 nM with 0.174 mM pyroGluProArgpNA; plasma kallikrein 1.9 nM with D-ProPheArgpNA; bovine trypsin 1.4 nM with 0.18 mM BzPheValArgpNA.

20 Citations

- (a) Sall DJ, JA Bastian, SL Briggs, JA Buben, NY Chirgadze, DK Clawson, ML Denny, DD Giera, DS Gifford-Moore, RW Harper, KL Hauser, VJ Klimkowski, TJ Kohn, H-  
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(b) Smith GF, TJ Craft, DS Gifford-Moore, WJ Coffman, KD Kurz, E Roberts, RT Shuman, GE Sandusky, ND Jones, N Chirgadze, and CV Jackson. A Family of Arginal Thrombin Inhibitors Related to Efegatran. *Sem. Thrombos. Hemost.* **22**, 5 173-183 (1996).

(c) Smith GF, DS Gifford-Moore, TJ Craft, N Chirgadze, KJ Ruterborries, TD Lindstrom, JH Satterwhite. Efegatran: A New Cardiovascular Anticoagulant. In *New Anticoagulants for the Cardiovascular Patient*. Ed. R Pifarre. Hanley & Belfus, Inc., Philadelphia (1997) pp 265-300.

(d) Sall DJ, JA Bastian, NY Chirgadze, ML Denny, MJ Fisher, DS Gifford-Moore, RW Harper, VJ Klimkowski, TJ Kohn, HS Lin, JR McCowan, ME Richett, GF Smith, K Takeuchi, JE Toth, M Zhang. Diamino Benzo[b]thiophene Derivatives as a Novel Class of Active Site Directed Thrombin Inhibitors: 5. Potency, Efficacy and Pharmacokinetic Properties of Modified C-3 Side Chain Derivatives. *In press, J Med Chem* (1999).

In general, the compounds of formula (I) exemplified in Part 1 of the Examples herein have been found to exhibit a Ki of 10  $\mu$ M or less in Assay 1 and/or a Kass of at least  $0.1 \times 10^6$  25 L/mole in Assay 2.

The ability of a test compound to elongate Partial Thromboplastin Time (Prothrombin Time) may be evaluated in the following test protocols.

30

Partial Thromboplastin Time (Prothrombin) Test Protocol

Venous blood was collected into 3.2% (0.109m) trisodium citrate vacutainer tubes at 1 volume of anticoagulant to nine volumes of blood. The blood cells were separated by centrifugation at 700g for ten minutes to yield plasma,  
5 which was frozen at 70°C until required.

To perform the test, 100µl of plasma was pipetted into in a glass test tube, 1µl of test compound in DMSO was added, and allowed to warm to 37° over two minutes. 100µl of warm (37°) Manchester (tissue thromboplastin) reagent (Helena  
10 Biosciences, UK) was added, allowed to equilibrate for two minutes. 100µl of warm (37°) 25mM calcium chloride solution was added to initiate clotting. The test tube was tilted three times through a 90° angle every five seconds to mix the reagents and the time to clot formation recorded. Data  
15 from a series of observations and test compound concentrations are analysed by a SAS statistical analysis program and a CT2 (Concentration required to double clotting time) for each compound is generated.  
  
20 Compounds of the invention were found to significantly elongate the partial thromboplastin time (Prothrombin time).

Example No.	Conc. necessary to double the prothrombin time ( $\mu\text{M}$ ) <sup>a</sup>
8	26
27	6.7
30	7.8
32	11
35	8.8
38	9.0
39	12
40	12
62	8.6
63	2.1
64	4.4
65	6.1

66	2.1 (average of 3 tests)
68	3.6
69	5.8
70	4.0

a The concentration quoted is that of the solution which, when added to the other reagents in the assay, doubles prothrombin time. The final concentration in the assay mixture is one third of this value.

By way of comparison with the result for the compound of Example 66, the compound of Example 75 of WO99/11657 was found to double prothrombin time at a concentration of 11.4 $\mu$ M (average of 3 tests).

By way of comparison with the result for the compound of Example 35, 1-aminoisoquinolin-7-oyl-D-phenylglycine-4-(4-fluoro-2-methanesulfonylphenyl)-piperazinamide ditrifluoroacetate salt (a compound within the scope of WO99/11657) was found to double prothrombin time at a concentration of 45 $\mu$ M (average of 3 tests).

#### Alternative Prothrombin Time and APTT Protocols

Coagulation Determinations. Prothrombin Times and APTT values were determined in HUMAN PLASMA with a STA instrument (Stago). BioPT is a special non-plasma clotting assay triggered with human tissue factor (Innovin). Possible binding to albumen or to lipid was assessed by comparing the BioPT effects in the presence/absence of 30 mg/ml human

albumen (HSA) and 1 mg/ml phosphatidyl choline (PC). Inhibitors were delivered in 50% MeOH vehicle.

**APTT ASSAY**

- 5    75 µl plasma Citrol *Baxter-Dade* Citrated Normal Human Plasma  
25 µl test sol'n  
75 µl Actin *Baxter-Dade* Activated Cephaloplastin incubate 2 min min. @ 37°  
10   75 µl CaCl<sub>2</sub> (0.02 M)

**PT ASSAY**

- 75 µl plasma  
25 µl test sol'n  
15   75 µl saline                incubate 1 min. @ 37° C  
75 µl Innovin *Baxter-Dade* Recombinant Human Tissue Factor

Compounds of the invention were found to be potent inhibitors of factor Xa.

20

**Examples - Part 2****Experimental:**

- 25   Abbreviations used follow IUPAC-IUB nomenclature. Additional abbreviations are HPLC, high-performance liquid chromatography; LC/MS, liquid chromatography / mass spectrometry; rt, retention time; NMR, nuclear magnetic resonance, TBTU, 2-(1H-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumtetrafluoroborate. Starting materials were purchased from Aldrich (Gillingham, UK), Lancaster

(Morecambe, UK), Avocado (Heysham, UK), Maybridge (Tintagel, UK), Nova Biochem (Nottingham, UK) or Bachem.

**Purification:**

5 Flash column chromatography was carried out using Merck silica gel Si60 (40-63 µm, 230-400 mesh). Purification of final products was by crystallisation, flash column chromatography or gradient reverse phase HPLC on a Waters Deltaprep 4000 at a flow rate of 50 mL/minute using a  
10 Deltapak C18 radial compression column (40 mm x 210 mm, 10-15 mm particle size). Eluant A consisted of aqueous trifluoroacetic acid (0.1 %) and eluant B 90% acetonitrile in aqueous trifluoroacetic acid (0.1 %) with gradient elution (Gradient, 0 minutes 5 % B for 1 minutes, then 5 % B  
15 to 20 % B over 4 minutes, then 20 % B to 60 % B over 32 minutes). Fractions were analysed by analytical HPLC and LC/MS before pooling those with >95 % purity for lyophilisation.

20 **Analysis:**

Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on a Bruker DPX300 (300 MHz). Analytical HPLC's were performed on a Shimadzu LC6 gradient system equipped with an autosampler. Eluant A consisted of aqueous  
25 trifluoroacetic acid (0.1 %) and eluant B consisted of 90 % acetonitrile and 10 % water, containing trifluoroacetic acid (0.1 %). Gradient 1 elution began at 5 % B and increased to 100 % B over seven minutes. Gradient 2 elution began at 5 % B and increased to 100 % B over ten minutes. Gradient 3  
30 elution began at 5 % B for one minute, increasing to 20 % B after the fourth minute, 40 % B after the 14<sup>th</sup> minute and then 100 % B after the 15<sup>th</sup> minute. The columns used were

Luna 2 C18 (3  $\mu$ , 30 mm x 4.6 mm), Luna 2 C18 (5  $\mu$ , 150 mm x 2 mm) and a Symmetry Rp8 (3.5  $\mu$ , 50 x 2.1 mm).

LC/MS were performed on a PESCIEX single quadrupole API-  
5 150EX instrument, equipped with a Luna 2 C18 column (3  $\mu$ , 30 mm x 4.6 mm) eluting with 20 % to 100 % acetonitrile in water over five minutes.

**Example 1****3-(Aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide bis(trifluoroacetate) salt**5   **2,6-Diaminobenzothiazole**

2-Amino-6-nitrobenzothiazole (500 mg, 2.56 mmol) was dissolved in methanol (20 mL) and 10 % palladium on carbon (50 mg) was added as a slurry in methanol (1 mL). The atmosphere was replaced with hydrogen and the suspension was stirred overnight. The catalyst was removed by suction filtration and the solvent evaporated to afford 2,6-diaminobenzothiazole (420 mg, 99 %) as a pale yellow solid.

**N-BOC-D-Phenylglycine 2-aminobenzothiazol-6-amide**

15   *N*-BOC-D-Phenylglycine (250 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg, 1.0 mmol) and 7-aza-1-hydroxybenzotriazole (140 mg, 1.0 mmol) were stirred in dimethylformamide (3 mL) for ten minutes. 2,6-Diaminobenzothiazole (160 mg, 1.0 mmol) was then added and the solution was stirred overnight at room temperature. Ethyl acetate (15 mL) was added and the solution was washed with water (5 mL), saturated citric acid solution (5 mL), saturated NaHCO<sub>3</sub> (5 mL) and water (5 mL), and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to afford *N*-BOC-D-phenylglycine 2-aminobenzothiazol-6-amide.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.93 (1 H, br s, C(O)NHAr); 7.72 (1 H, s, benzothiazole C(7)H); 7.35 (2 H, br s, Ph); 7.23 - 7.05 (3 H, m, Ph); 6.93 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 6.72 (1 H, d, J = 10 Hz, benzothiazole C(4)H or C(5)H); 6.05 (1 H, d, J = 7 Hz, CHPh); 5.92 (2 H, br s,

NH<sub>2</sub>) ; 5.45 (1 H, br s, BOCNH) ; 1.27 (9 H, s, <sup>t</sup>Bu).

**D-Phenylglycine 2-aminobenzothiazol-6-amide**

A solution of *N*-BOC-D-phenylglycine 2-aminobenzothiazol-5-amide in dichloromethane (5 mL) was treated with trifluoroacetic acid (5 mL) and stirred for 30 minutes. The dichloromethane and excess trifluoroacetic acid were removed under reduced pressure and the residue was triturated with diethyl ether to afford D-phenylglycine 2-aminobenzothiazol-6-amide as its trifluoroacetate salt (350 mg, 89 %).

**3-(Aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide trifluoroacetate salt**

*N*-BOC-3-aminomethylbenzoic acid (250 mg, 1.0 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (190 mg, 1.0 mmol) and 7-aza-1-hydroxybenzotriazole (140 mg, 1.0 mmol) were stirred in dimethylformamide (10 mL) for five minutes. D-Phenylglycine 2-aminobenzothiazol-6-amide trifluoroacetate salt (350 mg, 0.85 mmol) was then added and the mixture was stirred overnight. The solution was poured into ethyl acetate (20 mL) and washed with 5 % HCl (5 mL), saturated NaHCO<sub>3</sub> (5 mL) and water (5 mL), dried over MgSO<sub>4</sub> and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (60 % ethyl acetate / 40 % hexane to 100 % ethyl acetate) to afford *N*-BOC-3-(aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide. This was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) was added. The solution was stirred at room temperature for 30 minutes before the dichloromethane and excess trifluoroacetic acid were removed under reduced pressure. The residue was triturated with diethyl ether to

afford 3-(aminomethyl)benzoyl-D-phenylglycine 2-aminobenzothiazol-6-amide as its trifluoroacetate salt (150 mg, 32 %).

5       $^1\text{H}$  NMR ( $\text{d}_4$  MeOH): 8.21 ppm (1 H, s, benzothiazole C(7)H);  
7.97 (1 H, s, aminomethylbenzoyl C(2)H); 7.94 (1 H, d,  $J$  = 5 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.80 - 7.48 (5 H, m, Ar);  
7.47 - 7.32 (4 H, m, Ar); 5.81 (1 H, s, CHPh); 4.22 (2 H, s,  $\text{CH}_2\text{NH}_2$ ).

10     HPLC (Luna 2, Gradient 1): rt = 2.80 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.40 minutes, 432 (MH) $^+$ .

Examples 2 - 34 were prepared in the same fashion as Example 1, starting with the indicated nitro-compound or amine.

15     Other functional groups present were protected appropriately.

### **Example 2**

**3-(Aminomethyl)benzoyl-D-phenylglycine phenylamide**

20     **trifluoroacetate salt**

Prepared from aniline.

$^1\text{H}$  NMR ( $\text{d}_4$  MeOH): 7.85 ppm (2 H, br s, Ar); 7.49 (6 H, m, Ar); 7.27 (5 H, m, Ar) 7.01 (1 H, t,  $J$  = 9 Hz, Ar); 5.70 (1 H, s, CHPh); 4.12 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>).

25     HPLC (Luna 2, Gradient 1): rt = 3.59 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.99 minutes, 360 (MH) $^+$ .

### **Example 3**

**2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine**

30     **(1S,2S,3S,5R)-isopinocamphamide dihydrochloride salt**

Prepared from (1S,2S,3S,5R)-(+)-isopinocampheylamine.

$^1\text{H}$  NMR ( $\text{d}_4$  MeOH): 7.52 ppm (1 H, s, Ar-C(6)H); 7.42 (2 H, d,

*J* = 10, 2 x Ph-*o*-CH); 7.32 - 7.2 (3 H, m, 2 x Ph-*m*-CH, Ph-*p*-CH); 7.12 (1 H, d, *J* = 11 Hz, Ar-C(4)H); 6.67 (1 H, d, *J* = 11 Hz, Ar-C(3)H); 5.53 (1 H, s, NCH(Ph)); 4.18 (1 H, quintet, *J* = 8 Hz, ipc-C(1)H); 3.90 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.42 - 5 2.23 (2 H, m, ipc-C(3)H and ipc-(C(2)H); 1.91 (1 H, m, ipc-(C)6H); 1.80 (1 H, br s, ipc-(C)5H); 1.74 (1 H, t, *J* = 5 Hz, ipc-(C)6H); 1.32 (1 H, dd, *J* = 14, 8 Hz, ipc-C(7)H); 1.14 (3 H, s, ipc-C(8)H<sub>3</sub>); 1.02 (3 H, d, *J* = 8 Hz, ipc-C(10)H<sub>3</sub>); 0.95 (3 H, s, ipc-C(9)H<sub>3</sub>); 0.87 (1 H, d, *J* = 11 Hz, ipc-C(7)H).  
10 HPLC (Luna 2, Gradient 1): rt = 4.21 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 418 (MH-NH<sub>3</sub>)<sup>+</sup>.

**Example 4**

3-(Aminomethyl)benzoyl-D-phenylglycine quinolin-3-  
15 ylamide trifluoroacetate salt

Prepared from 3-aminoquinoline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 9.21 and 8.88 ppm (1 H each, s, quinoline C(2)H and C(4)H); 8.10 - 7.90 (4 H, m, Ar); 7.81 (1H, t, *J* = 7 Hz, Ar); 7.77 - 7.55 (5 H, m, Ar); 7.53 - 7.25 (3 H, m, Ar); 5.91 (1 H, s, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>).  
20 HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 411 (MH)<sup>+</sup>.

**Example 5**

25 3-(Aminomethyl)benzoyl-D-phenylglycine 4-(1-piperidyl)phenylamide trifluoroacetate salt

Prepared from 4-(1-piperidyl)aniline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.97 ppm (2 H, m, Ar); 7.8 (2 H, d, *J* = 9 Hz, Ar); 7.7 - 7.35 (9 H, m, Ar); 5.8 (1 H, s, CHPh); 4.2 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.55 (4 H, m, pip); 2.0 (4 H, m, pip); 1.8 (2 H, m. pip).  
30 HPLC (Luna 2, Gradient 1): rt = 2.81 minutes

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 443 (MH)<sup>+</sup>

**Example 6: 3-(Aminomethyl)benzoyl-D-phenylglycine 1-oxoindan-5-amide trifluoroacetate salt**

5 Prepared from 5-amino-1-oxoindane.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.98 ppm (1 H, s, (aminomethyl)benzoyl C(2)H); 7.96 ppm (1 H, d, J = 10 Hz, (aminomethyl)benzoyl C(6)H); 7.94 (1 H, s, indanone C(4)H); 7.70 - 7.52 (6 H, m, Ar); 7.47 - 7.33 (3 H, m, Ar); 5.84 (1 H, s, CHPh); 4.22 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.12 (2 H, t, J = 5 Hz, indanone C(3)H<sub>2</sub>); 2.82 - 2.75 (2 H, m, indanone C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 3.35 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 414 (MH)<sup>+</sup>.

15 **Example 7**

**3-(Aminomethyl)benzoyl-D-phenylglycine 3-cyano-4-methylphenyl-amide trifluoroacetate salt**

Prepared from 3-cyano-4-methylaniline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.01 ppm (1 H, s, 3-cyano-4-methylphenyl C(2)H); 7.98 (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d, J = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.72 - 7.52 (5 H, m, Ar); 7.48 - 7.28 (4 H, m, Ar); 5.82 (1 H, s, CHPh); 4.19 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.47 (3 H, s, CH<sub>3</sub>).

HPLC (Luna 2, Gradient 1): rt = 3.72 minutes.

25 LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 399 (MH)<sup>+</sup>.

**Example 8**

**3-(Aminomethyl)benzoyl-D-phenylglycine 4-amido phenylamide trifluoroacetate salt**

30 Prepared from 4-nitrobenzamide.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.20 - 8.05 ppm (2 H, m, 3-(aminomethyl)benzoyl C(2)H and C(6)H); 7.97 (2 H, d, J = 9

Hz, 4-(amidocarbonyl)phenyl C(2)H and C(6)H; 7.86 (2 H, d, J = 9 Hz, 4-(amidocarbonyl)phenyl C(3)H and C(5)H; 7.82 - 7.65 (4 H, m, Ar); 7.63 - 7.47 (3 H, m, Ar); 6.01, (1 H, s, CHPh); 4.32 (2 H, br s, CH<sub>2</sub>NH<sub>2</sub>).

5 HPLC (Symmetry C8, Gradient 2): rt = 4.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.51 minutes, 403 (MH)<sup>+</sup>.

#### Example 9

##### 3-(Aminomethyl)benzoyl-D-phenylglycine 3-

10 amidophenylamide trifluoroacetate salt

Prepared from 3-nitrobenzamide.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.30 ppm (1, s, 3-(amidocarbonyl)phenyl C(2)H); 8.17 (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.12 (1 H, d, J = 8 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.93 (1 H, d, J = 7 Hz, 3-(amidocarbonyl)phenyl C(6)H); 7.85 - 7.68 (5 H, m, Ar); 7.65 - 7.52 (4 H, m, Ar); 6.03 (1 H, s, CHPh); 4.37 (2 H, br s, CH<sub>2</sub>NH<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 403 (MH)<sup>+</sup>.

20

#### Example 10

##### 3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-

##### tetrahydro-1-oxonaphthyl-6-amide trifluoroacetate salt.

Prepared from 6-amino-1,2,3,4-tetrahydro-1-oxonaphthalene.

25 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.72 ppm (3 H, m, Ar); 7.40 (6 H, m, Ar); 7.20 (3 H, m, Ar); 5.65 (1 H, s, CHPh); 4.02 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.78 (2 H, t, J = 6 Hz, tetrahydronaphthyl C(4)H<sub>2</sub>); 2.42 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(2)H<sub>2</sub>); 1.95 (2H, m, tetrahydronaphthyl C(3)H<sub>2</sub>).

30 HPLC (Luna 2, gradient 1): rt = 3.57 minutes.

LC/MS (Luna 2, gradient 4): rt = 1.88 minutes; 428 (MH)<sup>+</sup>.

**Example 11****3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-tetrahydro-1-oxonaphthyl-7-amide trifluoroacetate salt**

Prepared from 7-nitro-1,2,3,4-tetrahydro-1-oxonaphthalene.

5   <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.04 ppm (1 H, s, tetrahydronaphthyl C(8)H); 7.82 (2 H, dd, J = 1, 10 Hz, Ar); 7.60 (2 H, dd, Ar); 7.45 (4 H, m, Ar); 7.28 (3 H, m, Ar); 7.16 (1 H, m, Ar); 5.68 (1 H, br s, CHPh); 4.03 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>), 2.83 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(4)H<sub>2</sub>); 2.40 (2 H, t, J = 7 Hz, tetrahydronaphthyl C(2)H<sub>2</sub>); 2.00 (2 H, m, tetrahydronaphthyl C(3)H<sub>2</sub>).

HPLC (Luna 2, gradient 1): rt = 3.65 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.94 minutes, 428 (MH)<sup>+</sup>.

15   **Example 12**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1,2,3,4-tetrahydro-naphthyl-6-amide trifluoroacetate salt**

Prepared from 6-amino-1,2,3,4-tetrahydronaphthalene.

10   <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.72 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.70 (1 H, d, J = 7 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.40 (4 H, m, Ar); 7.22 (3 H, m, Ar); 7.09 (1 H, m, Ar); 6.82 (1 H, m, Ar); 5.62 (1 H, s, CHPh); 4.00 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.50 (4 H, s,); 1.58 (4 H, s, tetrahydronaphthyl C(4)H<sub>2</sub> and C(5)H<sub>2</sub>).

25   HPLC (Luna 2, Gradient 4): rt = 4.21 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.21 minutes, 414 (MH)<sup>+</sup>.

**Example 13****3-(Aminomethyl)benzoyl-D-phenylglycine 4-(piperazin-1-yl)phenyl-amide bis(trifluoroacetate) salt**

Prepared from 4-(piperazin-1-yl)aniline.

10   <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.00 ppm (2 H, m, Ar); 7.70 - 7.35 (9 H, m,

Ar); 7.02 (2 H, d,  $J$  = 10 Hz, Ar); 5.80 (1 H, s, CHPh); 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.30 (8 H, m, pip).

HPLC (Luna 2, Gradient 1): rt = 2.71 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 444 (MH)<sup>+</sup>.

5

**Example 14**

**3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol**

**5-amide bis(trifluoroacetate) salt**

Prepared from 2,3-dihydro-5-nitroindole.

10 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.97 ppm (2 H, m, Ar); 7.82 (1 H, s, Ar); 7.65 (5 H, m, Ar); 7.45 (4 H, m, Ar); 5.80 (1 H, s, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.85 (2 H, t,  $J$  = 7.5 Hz, dihydroindole C(2)H<sub>2</sub>); 3.30 (2 H, t,  $J$  = 7.5 Hz, dihydroindole C(3)H<sub>2</sub>).

15 HPLC (Luna 2, Gradient 1): rt = 2.59 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 401 (MH)<sup>+</sup>.

**Example 15**

**3-(Aminomethyl)benzoyl-D-phenylglycine 4-chloro-3-**

20 **amidophenylamide trifluoroacetate salt**

Prepared from 2-chloro-5-nitrobenzamide.

10 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.98 ppm (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d,  $J$  = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.83 (1 H, s, 2-chloro-3-(amidocarbonyl)-phenyl C(6)H); 7.70 - 7.50 (5 H, m, Ar); 7.45 - 7.35 (4 H, m, Ar); 5.58 (1 H, s, CHPh); 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 3.09 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.62 minutes, 437/439 (MH)<sup>+</sup>.

30

**Example 16**

**3-(Aminomethyl)benzoyl-D-phenylglycine 3,5-**

**dichlorophenylamide trifluoroacetate salt**

Prepared from 3,5-dichloroaniline.

<sup>1</sup>H NMR ( $d_4$  MeOH): 7.98 ppm (1, s, 3-(aminomethyl)benzoyl C(2)H); 7.94 (1 H, d,  $J$  = 9 Hz, 3-(aminomethyl)benzoyl C(6)H); 7.73 - 7.51 (4 H, m, Ar); 7.64 (2 H, s, 3,5-dichlorophenyl C(2)H and C(6)H); 7.49 - 7.32 (3 H, m, Ar); 7.18 (1 H, s, 3,5-dichlorophenyl C(4)H); 5.80 (1 H, s, CHPh); 4.20 (2 H, s,  $\text{CH}_2\text{NH}_2$ ).

HPLC (Luna 2, Gradient 1): rt = 4.31 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.29 minutes, 428/430/432 (MH)<sup>+</sup>.

**Example 17****3-(Aminomethyl)benzoyl-D-phenylglycine 3-****(aminomethyl)phenyl-amide bis(trifluoroacetate) salt**

Prepared from 3-nitrobenzylamine.

<sup>1</sup>H NMR ( $d_4$  MeOH): 7.97 ppm (2 H, m Ar); 7.82 (1 H, s, Ar); 7.61 (5 H, m, Ar); 7.40 (4 H, m, Ar); 7.22 (1 H, d,  $J$  = 11 Hz, Ar); 5.81 (1 H, s, CHPh); 4.22 (2 H, s,  $\text{CH}_2\text{NH}_2$ ); 4.10 (2 H, s,  $\text{CH}_2\text{NH}_2$ ).

HPLC (Luna 2, Gradient 1): rt = 2.67 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 389 (MH)<sup>+</sup>.

**Example 18****3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-****dimethylindol-5-amide bis(trifluoroacetate) salt**

Prepared from 2,3-dimethyl-5-nitroindole.

<sup>1</sup>H NMR ( $d_3$  acetonitrile): 9.12 ppm (1 H, br s, NH); 9.08 (1 H, bs, NH); 8.40 (1 H, d,  $J$  = 7 Hz, Ar), 8.20 (1 H, s, Ar); 8.0 (1 H, d,  $J$  = 7 Hz, Ar); 7.88-7.50 (7 H, m, Ar); 7.30 (2 H, m, Ar); 6.0 (1 H, d,  $J$  = 6.5 Hz, CHPh); 4.30 (2 H, s,  $\text{CH}_2\text{NH}_2$ ); 2.71 (2 H, br s,  $\text{CH}_2\text{NH}_2$ ); 2.50 (3 H, s, indole

C(3)CH<sub>3</sub>) ; 2.31 (3 H, s, indole C(2)CH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 3.76 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.99 minutes, 427 (MH)<sup>+</sup>.

5   **Example 19**

**3-(Aminomethyl)benzoyl-D-phenylglycine 4-chlorophenylamide trifluoroacetate salt**

Prepared from 4-chloroaniline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.97 ppm (2 H, m, Ar); 7.70 - 7.50 (13 H,

10 m, Ar); 5.80 (1 H, s, CHPh); 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) .

HPLC (Luna 2, Gradient 1): rt = 3.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 394 (MH)<sup>+</sup>.

**Example 20**

**1-[3-(Aminomethyl)benzoyl-D-phenylglycyl]piperidine trifluoroacetate salt**

Prepared from piperidine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.97 ppm (2 H, m Ar); 7.65 - 7.30 (7 H, m, Ar); 6.10 (1 H, s, CHPh); 4.21 (2H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 3.79 (1H, m, pip); 3.50 (3H, m, pip); 1.70 - 1.21 (5 H, m, pip) .

HPLC (Luna 2, Gradient 1): rt = 3.36 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.78 minutes, 394 (MH)<sup>+</sup>.

**Example 21**

**1-[3-(Aminomethyl)benzoyl-D-phenylglycyl]-3-[(N-ethyl-N-methyl)amido]piperidine trifluoroacetate salt**

Prepared from 3-[(N-ethyl-N-methyl)amidocarbonyl] - piperidine.

<sup>1</sup>H NMR (CD<sub>3</sub>CN): The compound contains two chiral centres and

30 is therefore a mixture of diastereomers, as well as exhibiting rotamers due to the N-ethyl-N-methyl amide. 8.45 - 7.78 ppm (5 H, m, Ar and NH); 7.72 - 7.28 (5 H, m, Ph);

6.10 - 5.90 (1 H, m, CHPh); 4.61 - 4.35 (1 H, m, piperidine H); 4.14 (2 H, br s, CH<sub>2</sub>NH<sub>2</sub>); 3.97 - 3.66 (1 H, m, piperidine H); 3.50 - 2.35 (12 H, m) 1.90 - 0.75 (4 H, m).

HPLC (Luna 2, Gradient 1): rt = 3.13 minutes.

5 LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 437 (MH)<sup>+</sup>.

### Example 22

#### **1-[3-(Aminomethyl)benzoyl-D-phenylglycanyl] pyrrolidine trifluoroacetate salt**

10 Prepared from pyrrolidine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.95 ppm (2 H, m, Ar); 7.72-7.34 (7 H, m, Ar); 5.91 (1 H, m, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.80 (2 H, m, pyr); 3.61 (2 H, m, pyr); 3.50 (2 H, m, pyr); 3.19 (2 H, m, pyr).

15 HPLC (Luna 2, Gradient 1): rt = 3.06 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.57 minutes, 338 (MH)<sup>+</sup>.

### Example 23

#### **2-[3-(Aminomethyl)benzoyl-D-phenylglycanyl] decahydroisoquinoline trifluoroacetate salt**

20 Prepared from decahydroisoquinoline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.70 ppm (2 H, br s, Ar); 7.41 - 7.09 (7 H, m, Ar); 5.95-5.78 (1H, m, CHPh); 3.95 (2H, s, CH<sub>2</sub>NH<sub>2</sub>); 1.7 - 0.65 (16 H, m, decahydroisoquinoline C(H)'s).

25 HPLC (Luna 2, Gradient 1): rt = 4.11 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 406 (MH)<sup>+</sup>.

### Example 24

#### **3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol-**

30 **6-amide trifluoroacetate salt**

Prepared from 2,3-dihydro-6-nitroindole.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.91 ppm (2 H, m, Ar); 7.75 (1 H, s, Ar);

7.57 (4 H, m, Ar); 7.34 (5 H, m, Ar); 5.75 (1 H, s, CHPh);  
4.15 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.75 (2 H, t, J = 7.5 Hz,  
dihydroindole C(2)H<sub>2</sub>); 3.20 (2 H, t, J = 7.5 Hz,  
dihydroindole C(3)H<sub>2</sub>).

5 HPLC (Luna 2, Gradient 1): rt = 2.54 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.24 minutes, 401 (MH)<sup>+</sup>.

### Example 25

#### 3-(Aminomethyl)benzoyl-D-phenylglycine 2,3-

10 dihydroindolamide trifluoroacetate salt

Prepared from 2,3-dihydroindole.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.92 ppm (1 H, d, J = 7 Hz, NH); 8.22 (1 H, d, J = 9.5 Hz, dihydroindole C(7)H); 7.97 (2 H, m, Ar);  
7.48 (3 H, m, Ar); 7.19 (2 H, m, Ar); 7.08 (1 H, m, Ar);  
15 6.02 (1 H, m, CHPh); 4.41 (1 H, m, dihydroindole C(2)H);  
4.19 (2H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.78 (1H, m, dihydroindole C(2)H); 3.23  
(1H, m, dihydroindole C(3)H); 3.07 (1H, m, dihydroindole  
C(3)H).

HPLC (Luna 2, Gradient 1): rt = 3.79 minutes.  
20 LC/MS (Luna 2, gradient 4): rt = 2.21minutes, 386 (MH)<sup>+</sup>.

### Example 26

#### 3-(Aminomethyl)benzoyl-D-phenylglycine 1-methyl-2,3-

#### dihydro-indol-6-amide bis(trifluoracetate salt)

25 Prepared from 6-amino-2,3-dihydro-1-methylindole.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.0 ppm (2 H, m, Ar); 7.65 (4 H, m, Ar);  
7.40 (3 H, m, Ar); 7.15 (2 H, m, Ar); 6.95 (1 H, m, Ar);  
5.83 (1 H, s, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.42 (2 H, m,  
dihydroindole C(2)H); 2.98 (2H, m, dihydroindole C(3)H);  
30 2.82 (3H, s, NCH<sub>3</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.80 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.88 minutes, 415 (MH)<sup>+</sup>.

**Example 27**

**3-(Aminomethyl)benzoyl-D-phenylglycine 3-acetyl amino-4-methylphenylamide trifluoroacetate salt**

5 Prepared from 2-methyl-5-nitroacetanilide.

<sup>1</sup>H NMR (D<sub>2</sub>O) : 7.78 - 7.19 (12 H, m, Ar), 5.64 (1H, s, α-CH), 4.17 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>), 2.12 (6H, s, 2 x CH<sub>3</sub>)

HPLC (Luna 2, Gradient 1): rt = 3.10 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.56 minutes, 431 (MH<sup>+</sup>).

10

**Example 28**

**3-(Aminomethyl)benzoyl-D-phenylglycine (R/S)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamide trifluoroacetate salt**

Prepared from (R/S)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine, synthesised as described below.

**(R/S)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine**

A suspension of methyltriphenylphosphonium iodide (680 mg, 1.68 mmol) in tetrahydrofuran (7 mL) was cooled to -45°C. n-Butyllithium (1.0 mL, 1.6 M in hexane, 1.60 mmol) was then added dropwise, and the solution was stirred for 1 hour. 1,2,3,4-Tetrahydro-7-nitro-1-oxonaphthalene (200 mg, 1.05 mmol) in tetrahydrofuran (3 mL) was then added over 5 minutes. The reaction mixture was allowed to warm to room temperature before being quenched with water (20 mL). The solution was then extracted with dichloromethane (2 x 25 mL), the solvent was dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to give a black oil. The crude product was then purified by flash chromatography (ethyl acetate / hexane; 1:40) to afford 5,6,7,8-tetrahydro-8-methylene-2-nitro-naphthalene as a white solid (150 mg, 76%).

A solution of the olefin (100 mg, 0.53 mmol) in methanol (2

mL) was stirred over 10% palladium on carbon (20 mg). The mixture was purged with hydrogen and stirred for 18 hrs under a balloon of hydrogen. The reaction mixture was then filtered through celite, washing with additional methanol, 5 and concentrated under reduced pressure to afford (R/S)-8-methyl-5,6,7,8-tetrahydronaphth-2-ylamine as a colourless oil (75 mg, 82%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.53 ppm (1 H, d, J = 8 Hz, C(4)H); 7.21 (1 H, d, J = 2 Hz, C(1)H); 7.18 (1 H, dd, J = 8, 2 Hz, C(3)H); 10 4.16 (2 H, br s, NH<sub>2</sub>); 3.52 (1 H, sextet, J = 7 Hz, CHCH<sub>3</sub>); 3.41-3.25 (2 H, m, C(5)H<sub>2</sub>); 2.61-2.45 (2 H, m, tetrahydro-naphthalene C(6)H and/or C(7)H); 2.43-2.32 (1 H, m, tetrahydronaphthalene C(6) or C(7)H); 2.23-2.12 (1 H, m, tetrahydronaphthalene C(6)H or C(7)H); 1.96 (3 H, d, J = 7 Hz, CH<sub>3</sub>). 15

**3-(Aminomethyl)benzoyl-D-phenylglycine (R/S)-8-methyl-5,6,7,8-tetrahydro-naphth-2-ylamide trifluoroacetate salt.**

<sup>1</sup>H NMR (MeOH): 7.95 ppm (2 H, br s, Ar); 7.76 - 7.60 (4 H, m, Ar); 7.48 - 7.31 (4 H, m, Ar); 7.29 - 7.21 (1 H, m, Ar); 6.97 (1 H, d, J = 8 Hz, Ar); 5.80 (1 H, s, CHPh); 4.18 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.90 - 2.69 (3 H, m, tetrahydronaphthalene C(5)H and C(8)H<sub>2</sub>); 1.99-1.80 (2 H, m, tetrahydronaphthalene C(6)H and/or C(7)H); 1.75 - 1.63 (1 H, m, tetrahydronaphthalene C(6) or C(7)H); 1.58 - 1.40 (1 H, m, tetrahydro-naphthalene C(6)H or C(7)H); 1.27 (3 H, d, J = 7 Hz, CH<sub>3</sub>). 25

HPLC (Symmetry, Gradient 2): rt = 6.73 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.53 minutes, 428 (MH)<sup>+</sup>.

30 **Example 29**

**3-(Aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide trifluoroacetate salt**

Prepared from 5-aminoindane.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.16 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.15 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.96 - 7.54 (8 H, m, Ar); 7.45 (1 H, d, J = 8 Hz, indane C(6)H or C(7)H); 7.33 (1 H, d, J = 8 Hz, indane C(6)H or C(7)H); 6.0 (1 H, s, CHPh); 4.39 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.06 (4 H, q, J = 7 Hz, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.26 (2 H, quintet, J = 7 Hz, indane C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.02 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.42 minutes, 400 (MH)<sup>+</sup>.

### Example 30

#### 3-(Aminomethyl)benzoyl-D-phenylglycine 4-isopropylphenylamide trifluoroacetate salt

Prepared from 4-isopropylaniline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.17 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 8.15 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.83 - 7.59 (9 H, m, Ar); 7.38 (2 H, d, J = 8.5 Hz, Ar); 6.0 (1 H, s, CHPh); 4.38 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.09 (1 H, septet, J = 7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>); 1.42 (6 H, d, J = 7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.21 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.48 minutes, 402 (MH)<sup>+</sup>.

### Example 31

#### 3-(Aminomethyl)benzoyl-D-phenylglycine (1S,2S,3S,5R)-isopinocampamide trifluoroacetate salt

Prepared from (1S,2S,3S,5R)-(+)-isopinocampheylamine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 7.96 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.95 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.67 - 7.25 (7 H, m, Ar); 5.70 (1 H, s, CHPh); 4.28 (1 H, m, isopinocampheyl C(1)H); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.55 - 1.77 (5 H, m, isopinocampheyl H's); 1.26 (3 H, s, CH<sub>3</sub>); 1.14 (3 H,

d,  $J = 7\text{Hz}$ , isopinocampheyl C(10)H<sub>3</sub>) ; 1.08 (3 H, s, CH<sub>3</sub>) ; 1.04 - 0.94 (2 H, m, isopinocampheyl H's).

HPLC (Luna 2, Gradient 1): rt = 4.34 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.34 minutes, 420 (MH)<sup>+</sup>.

5

**Example 32**

**3-(Aminomethyl)benzoyl-D-phenylglycine 4-(1-hydroxyethyl)phenylamide trifluoroacetate salt**

Prepared from 1-(4-aminophenyl)ethanol.

10 <sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 7.85 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H) ; 7.84 (1 H, m, 3-(aminomethyl)benzoyl C(6)H) ; 7.56 - 7.05 (11 H, m, Ar) ; 5.72 (1 H, s, CHPh) ; 4.69 (1 H, q,  $J = 6.5\text{ Hz}$ , CH(OH)CH<sub>3</sub>) ; 4.08 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 1.31 (3 H, d,  $J = 6.5\text{ Hz}$ , CH<sub>3</sub>).

15 HPLC (Luna 2, Gradient 1): rt = 3.0 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 404 (MH)<sup>+</sup>.

**Example 33**

**3-(Aminomethyl)benzoyl-D-phenylglycine cis-2-**

20 **aminocyclohexyl-amide bis(trifluoroacetate) salt**

Prepared from *cis*-1,2-diaminocyclohexane.

1<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.08 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H) ; 8.06 (1 H, m, 3-(aminomethyl)benzoyl C(6)H) ; 7.79 - 7.48 (7 H, m, Ar) ; 5.87 (1 H, s, CHPh) ; 4.46 (1 H, m, cyclohexyl C(1)H) ; 4.30 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 3.54 (1 H, m, cyclohexyl C(2)H) ; 2.11 - 1.52 (8 H, m, cyclohexyl H's).

HPLC (Luna 2, Gradient 1); rt = 2.40 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.08 minutes, 381 (MH)<sup>+</sup>.

30 **Example 34**

**1-[3-(Aminomethyl)benzoyl-D-phenylglycyl] 4-hydroxypiperidine hydrochloride salt**

Prepared from 4-hydroxypiperidine.

<sup>1</sup>H NMR ( $d_4$  MeOH) : 7.84 ppm (1 H, s, 3-(aminomethyl)benzoyl C(2)H); 7.80 (1 H, m, 3-(aminomethyl)benzoyl C(6)H); 7.59 - 7.17 (7 H, m, Ar); 6.03 (1 H, s, CHPh); 4.11 (2 H, s, 5  $\text{CH}_2\text{NH}_2$ ); 3.90 (1 H, m, piperidyl C(4)H); 3.62 (2 H, m, piperidyl C(2)H and C(6)H); 3.14 - 2.94 (2 H, m, piperidyl C(2)H and C(6)H); 1.93 - 1.16 (4 H, m, piperidyl C(3)H<sub>2</sub> and C(5)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.56 minutes.

10 LC/MS (Luna 2, Gradient 4): rt = 1.36 minutes, 368 (MH)<sup>+</sup>.

### Example 35

#### 3-(Aminomethyl)benzoyl-D-phenylglycine 1-acetyl-2,3-dihydro-indol-6-amide trifluoroacetate salt

15 **1-Benzylloxycarbonyl-2,3-dihydro-6-nitroindole**  
A solution of 6-nitroindoline (10.0 g, 0.061 mol), triethylamine (22.7 mL, 0.16 mol) and dimethylaminopyridine (50 mg, cat.) in dichloromethane (130 mL) was stirred at 0°C and benzyl chloroformate (18 mL, 0.12 mol) was added slowly. The mixture was allowed to warm to room temperature overnight. The mixture was washed with water (50 mL), 5% aqueous HCl (100 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL) and water (50 mL). The dichloromethane was dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give an orange solid. This was triturated in diethyl ether (150 ml) to give a yellow solid (12.34 g, 68%).

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.80 ppm (1 H, dd,  $J$  = 8, 2 Hz, C(7)H); 7.35 (5 H, m, Ph); 7.20 (2 H, m, C(4)H and C(5)H); 5.25 (2 H, br s, CH<sub>2</sub>Ph); 4.11 (2 H, t,  $J$  = 8 Hz, dihydroindole C(2)H<sub>2</sub>); 3.15 (2 H, t,  $J$  = 8 Hz, dihydroindole C(3)H<sub>2</sub>).

**6-amino-1-benzyloxycarbonyl-2,3-dihydroindole**

A mixture of 1-benzyloxycarbonyl-2,3-dihydro-6-nitroindole (1.0 g, 3.36 mmol) and tin(II) chloride dihydrate (3.78 g, 16.75 mmol) in ethanol (70 mL) was heated at 70°C, under an atmosphere of nitrogen, for 3 hours. The solution was cooled and the solvent evaporated under reduced pressure to give an off-white solid. The solid was partitioned between water (50 mL) and ethyl acetate (100 mL) and the aqueous layer basified (pH 11) with 1M sodium hydroxide solution. The mixture was 5 filtered to remove tin salts and the ethyl acetate was separated, dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to give the amine as a yellow oil (0.89 g, 99 %).  
 $^1\text{H NMR}$  ( $\text{CDCl}_3$ ): 7.51 - 7.33 ppm (6 H, m, Ph + C(7)H); 6.93 (1 H, d,  $J = 8$  Hz, C(4)H); 6.32 (1 H, dd,  $J = 8, 2$  Hz, C(5)H); 10 5.28 (2 H, br s,  $\text{CH}_2\text{Ph}$ ); 4.01 (2 H, t,  $J = 7.5$  Hz, dihydroindole C(2)H<sub>2</sub>); 3.66 (2 H, bs, NH<sub>2</sub>); 3.05 (2 H, t,  $J = 7.5$  Hz, dihydroindole C(3)H<sub>2</sub>).  
15

**N-BOC-D-phenylglycine 1-benzyloxycarbonyl-2,3-dihydroindol-20 6-amide**

A solution of *N*-BOC-D-phenylglycine (0.83 g, 3.28 mmol), 1-[3-(dimethyl-amino)propyl]-3-ethylcarbodiimide hydrochloride (0.75 g, 3.9 mmol), 1-hydroxy-7-azabenzotriazole (0.54 g, 3.9 mmol) and 4-(*N,N*-dimethylamino)pyridine (10 mg, cat.) in 25 dimethylformamide (20 mL) was stirred at room temperature and a solution of the above amine (0.88 g, 3.28 mmol) in dimethylformamide (20 mL) was added and the mixture allowed to stir overnight. The dimethylformamide was evaporated under reduced pressure and the resulting oil partitioned between water (50 mL) and ethyl acetate (50 mL). The ethyl acetate was washed with 5% aqueous HCl (10 mL) and saturated aqueous  $\text{NaHCO}_3$  (10 mL), dried ( $\text{MgSO}_4$ ) and evaporated under 30

reduced pressure to give the amide as a golden foam (1.6 g, 97 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.43 - 7.10 ppm (13 H, m, Ar): 6.85 (1 H, d, J = 6 Hz, NH); 5.61 (1 H, br s, NH); 5.03 (2 H, br s, CH<sub>2</sub>Ph); 3.85 (2 H, t, J = 7 Hz, dihydroindole C(2)H<sub>2</sub>); 2.85 (2 H, t, J = 8 Hz, dihydroindole C(3)H<sub>2</sub>); 1.19 (9 H, s, <sup>t</sup>Bu).

**D-phenylglycine 1-benzyloxycarbonyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

10 Trifluoroacetic acid (5 mL) was added to a solution of the above foam in dichloromethane (20 mL) and the solution was allowed to stir for 2 hours at room temperature. The solvent was evaporated under reduced pressure to give the amine trifluoracetate salt as a red foam (1.5 g, 91 %) which was used without further purification.

**3-(N-BOC-Aminomethyl)benzoyl-D-phenylglycine (1-benzyloxycarbonyl-2,3-dihydro)-indol-6-amide**

A solution of 3-(N-BOC-aminomethyl)benzoic acid (0.798 g, 3.2 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.73 g, 3.8 mmol), 1-hydroxy-7-azabenzotriazole (0.52 g, 3.8 mmol) and triethylamine (1.0 mL, 7.2 mmol) in dimethylformamide (10 mL) was stirred at room temperature and a solution of the above amine (1.5 g, 3.0 mmol) in dimethylformamide (5 mL) was added. The mixture was stirred overnight before the dimethylformamide was evaporated under reduced pressure, and the resulting oil partitioned between water (50 mL) and ethyl acetate (50 mL). The ethyl acetate layer was washed with 5% aqueous HCl (10 mL) and saturated aqueous NaHCO<sub>3</sub> (10 mL), dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to give a yellow solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.75 - 7.22 ppm (17 H, m, Ar): 7.05 (1 H, d,

$J = 5.5$  Hz, NH); 5.74 (1H, d,  $J = 6$  Hz, CHPh); 5.21 (2 H, s, OCH<sub>2</sub>Ph); 4.89 (1 H, br s, NH); 4.32 (2 H, d,  $J = 6$  Hz, CH<sub>2</sub>NHBOC); 4.02 (2H, t,  $J = 8$  Hz, dihydroindole C(2)H<sub>2</sub>); 3.05 (2H, t,  $J = 8$  Hz, dihydroindole C(3)H<sub>2</sub>); 1.4 (9 H. s, <sup>t</sup>Bu).

5

**3 - (N-BOC-Aminomethyl)benzoyl-D-phenylglycine 2,3-dihydroindol-6-amide**

A solution of the above solid in methanol (50 mL) was stirred over 10%Pd/C (500 mg) under an atmosphere of H<sub>2</sub> and 10 heated under reflux for 2 hours. The mixture was cooled, filtered and the solvent evaporated under reduced pressure to provide the unprotected dihydroindole as a yellow foam (1.4g, 88%) which was used without further purification.

15 **3 - (Aminomethyl)benzoyl-D-phenylglycine 1-acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

A solution of the dihydroindole (500 mg, 1.0 mmol) and triethylamine (0.28 mL, 2 mmol) in dichloromethane (20 mL) was stirred at 0°C and acetyl chloride (86 mg, 1.1 mmol) was 20 added dropwise, then left to stir overnight. The mixture was washed with 5% aqueous HCl (10 mL) and the organic phase was dried (MgSO<sub>4</sub>) and evaporated. The residue was purified by flash column chromatography (ethyl acetate / hexane, 1:1) to give a yellow oil. The oil was dissolved in dichloromethane 25 (20 mL) and treated with trifluoroacetic acid (5 mL). After stirring for 2 hours the solvent was evaporated under reduced pressure to an oil, which after triturating with diethyl ether gave the amine as its trifluoroacetate salt as a white solid (337 mg, 61 %).

30 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.30 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.60 (4 H, m, Ar); 7.39 (4 H, 3, m, Ar); 7.22 (1 H, d,  $J = 10$  Hz, Ar); 5.82 (1 H, s, CHPh); 4.2 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.15

(2 H, t, J = 7 Hz, dihydroindole C(2)H<sub>2</sub>) ; 3.17 (2 H, t, J = 7 Hz, dihydroindole C(3)H<sub>2</sub>) ; 2.25 (3 H, s, CH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 3.39 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 443 (MH)<sup>+</sup>.

5

Examples 36 - 60 were prepared from the intermediate 3-(N-BOC-aminomethyl)-benzoyl-D-phenylglycine 2,3-dihydroindol-5-amide, described for Example 29, and the appropriate carboxylic acid or derivative, using standard chemical methods and protecting other functionality where required.

#### Example 36

##### **3-(Aminomethyl)benzoyl-D-phenylglycine 1-propanoyl-2,3-dihydro-indol-6-amide trifluoroacetate salt**

15 Prepared using propanoyl chloride.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.58 ppm (1 H, d, J = 1.2 Hz, dihydroindole C(7)H) ; 8.18 (2 H, m, Ar) ; 7.82 (4 H, m, Ar) ; 7.59 (4 H, m, Ar) ; 7.37 (1 H, m, Ar) ; 6.03 (1 H, s, CHPh) ; 4.39 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 4.31 (2 H, t, J = 9 Hz, dihydroindole C(2)H) ; 3.37 (2 H, t, J = 9 Hz, dihydroindole C(3)H) ; 2.73 (2 H, q, J = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>) ; 1.47 (3 H, t, J = 7.5 Hz, CH<sub>2</sub>CH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 3.55 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.94 minutes, 457 (MH)<sup>+</sup>.

25

#### Example 37

##### **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-methylpropanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt**

30 Prepared using 2-methylpropanoyl chloride.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.32 ppm (1 H, s, dihydroindole C(7)H) ; 7.98 (2 H, m, Ar) ; 7.60 (4 H, m, Ar) ; 7.43 (4 H, m, Ar) ;

7.18 (1 H, m, Ar); 5.83 (1 H, s, CHPh); 4.21 (4 H, m, CH<sub>2</sub>NH<sub>2</sub> and dihydroindole C(2)H); 3.18 (2 H, t, J = 9 Hz, dihydroindole C(3)H), 2.95 (1 H, m, CH(CH<sub>3</sub>)<sub>2</sub>); 1.22 (6 H, d, J = 8 Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

5 HPLC (Luna 2, Gradient 1): rt = 3.74 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 471 (MH)<sup>+</sup>.

### Example 38

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-alaninoyl-**

10 **2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using D-alanine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.40 ppm (1 H, s, Ar); 8.01 (2 H, m, Ar); 7.65 (4 H, m, Ar); 7.45 (4 H, m, Ar); 7.25 (1 H, d, J = 10 Hz, Ar); 5.85 (1 H, s, CHPh); 4.4 (1 H, q, J = 7 Hz, alaninyl CHNH<sub>2</sub>); 4.25 (2 H, s, ArCH<sub>2</sub>NH<sub>2</sub>); 4.25 (2 H, t, J = 8 Hz, dihydroindole C(2)H<sub>2</sub>); 3.28 (2 H, t, J = 8 Hz, dihydroindole C(3)H<sub>2</sub>); 1.65 (3 H, d, J = 7 Hz, CH<sub>3</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.85 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 472 (MH)<sup>+</sup>.

20

### Example 39

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-alaninoyl-**

**2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using L-alanine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.43 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.63 (4 H, m, Ar); 7.45 (4 H, m, Ar); 7.25 (1 H, d, J = 10 Hz, Ar); 5.85 (1 H, s, CHPh); 4.35 (1 H, q, J = 7 Hz, alaninyl CHNH<sub>2</sub>); 4.25 (2 H, t, J = 7.5 Hz, indoline C(2)H<sub>2</sub>); 4.2 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.25 (2 H, t, J = 8 Hz, indoline C(3)H<sub>2</sub>); 1.6 (3 H, d, J = 7 Hz, CH<sub>3</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 472 (MH)<sup>+</sup>.

**Example 40**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(N-acetyl-D-alaninoyl)-2,3-dihydroindol-6-amide trifluoroacetate**

5   **salt**

Prepared using *N*-acetyl-D-alanine.

<sup>1</sup>H NMR ( $d_4$  MeOH) : 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.61 (4 H, m, Ar); 7.40 (4 H, m, Ar); 7.18 (1 H, d,  $J$  = 9 Hz, Ar); 5.83 (1 H, s, CHPh); 4.70 (1 H, br m, CHNHAc); 4.38 (1 H, m, indoline C(2)H); 4.21 (2H, s,  $CH_2NH_2$ ); 4.20 (1 H, t,  $J$  = 8 Hz indoline C(2)H); 3.2 (2 H, t,  $J$  = 8 Hz, indoline C(3)H<sub>2</sub>); 2.01 (3 H, s, COCH<sub>3</sub>); 1.4 (3 H, d,  $J$  = 7 Hz, CH<sub>3</sub>).  
HPLC (Luna 2, Gradient 1): rt = 3.24 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 514 (MH)<sup>+</sup>.

15

**Example 41**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(N-acetyl-L-alaninoyl)-2,3-dihydroindol-6-amide trifluoroacetate**

**salt**

20   Prepared using *N*-acetyl-L-alanine.

<sup>1</sup>H NMR ( $d_4$  MeOH) : 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.62 (4 H, m, Ar); 7.38 (4 H, m, Ar); 7.18 (1 H, d, Ar); 5.83 (1 H, s, CHPh); 4.70 (1 H, m, CHNHAc); 4.35 (1 H, m, dihydroindole C(2)H); 4.2 (2H, s,  $CH_2NH_2$ ); 4.2 (1H, m, dihydroindole C(2)H); 3.2 (2 H, t,  $J$  = 8 Hz, dihydroindole C(3)H<sub>2</sub>); 2.0 (3 H, s, COCH<sub>3</sub>); 1.4 (3 H, d,  $J$  = 7 Hz, CH<sub>3</sub>).  
HPLC (Luna 2, Gradient 1): rt = 3.19 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.67 minutes, 514 (MH)<sup>+</sup>.

30   **Example 42**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-aminoacetyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using glycine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.41 (1 H, s, dihydroindole C(7)H); 7.97 (2 H, br s, Ar); 7.58 (4 H, m, Ar); 7.22 (1 H, d, J = 8 Hz, Ar); 5.84 (1 H, s, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.15 (2 H, t, J = 9 Hz, dihydroindole C(2)H); 4.04 (2 H, s, COCH<sub>2</sub>NH<sub>2</sub>); 3.23 (2H, t, J = 9 Hz, dihydroindole C(3)H).

HPLC (Luna 2, Gradient 1): rt = 2.77 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.24 minutes, 458 (MH)<sup>+</sup>.

10 **Example 43**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-methylbutanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using 3-methylbutanoyl chloride.

15 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.40 ppm (1 H, s, Ar); 8.02 (2 H, m, Ar); 7.67 (4 H, m, Ar); 7.22 (1 H, d, J = 11 Hz, Ar); 5.90 (1 H, s, CHPh); 4.27 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.22 (2 H, t, J = 8 Hz, indoline C(2)H<sub>2</sub>); 3.22 (2H, t, J = 8 Hz, indoline C(3)H<sub>2</sub>); 2.45 (2 H, d, J = 7 Hz, COCH<sub>2</sub>); 2.28 (1 H, septet, J = 7 Hz, CHMe<sub>2</sub>); 1.1 (6 H, d, J = 7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.18 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 485 (MH)<sup>+</sup>.

**Example 44**

25 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(benzyloxy)-acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using 2-benzyloxyacetyl chloride.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.40 ppm (1 H, s, Ar); 8.02 (2 H, m, Ar); 7.65 (5 H, m, Ar); 7.45 (10 H, m, Ar); 7.22 (1 H, d, J = 10 Hz, Ar); 5.91 (1 H, s, CHPh); 4.73 (2 H, s, COCH); 4.35 (1 H, q, CHNH<sub>2</sub>); 4.37 (2 H, s, CH<sub>2</sub>Ph); 4.25 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.12 (2 H, t, J = 7.5 Hz, indoline C(2)H<sub>2</sub>); 3.2 (2 H, t, J =

7.5 Hz, indoline C(3)H<sub>2</sub>) .

HPLC (Luna 2, Gradient 1): rt = 4.25 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.15 minutes, 549 (MH)<sup>+</sup>.

5   **Example 45**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-threoninoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using L-threonine.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.31 ppm (1 H, s, Ar); 7.80 (2 H, m, Ar);

10 7.45 (4 H, m, Ar); 7.25 (4 H, m, Ar); 7.05 (1 H, d, Ar);

5.65 (1 H, s, CHPh); 4.10 (2 H, t, J = 8 Hz, indoline

C(2)H<sub>2</sub>); 4.02 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.11 (2 H, t, J = 8 Hz,

indoline C(3)H<sub>2</sub>); 1.21 (3H, d, CH<sub>3</sub>); other signals obscured by solvent.

15 HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.65 minutes, 502 (MH)<sup>+</sup>.

**Example 46**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-prolinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using L-proline.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.47 ppm (1 H, s, Ar); 8.05 (2 H, m, Ar);

7.75 - 7.65 (4 H, m, Ar); 7.56 - 7.47 (4 H, m, Ar); 7.30 (1

25 H, d, J = 9 Hz, Ar); 5.91 (1 H, s, CHPh); 4.73 (1 H, t, J =

6.5 Hz, proline C(2)H); 4.25 (4 H, m, CH<sub>2</sub>NH<sub>2</sub> and indoline

C(2)H<sub>2</sub>); 3.65-3.32 (3 H, m, indoline C(3)H<sub>2</sub> and proline

C(5)H); 2.70 (1 H, m, proline C(5)H); 2.33 - 2.15 (4 H, m,

proline C(3)H<sub>2</sub> and C(4)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.

30 LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 498 (MH)<sup>+</sup>.

**Example 47**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-((S)-2-hydroxypropanoyl)-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using (S)-2-hydroxypropanoic acid.

5   <sup>1</sup>H NMR ( $d_4$  MeOH): 8.33 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.66 - 7.56 (4 H, m, Ar); 7.45 - 7.37 (4 H, m, Ar); 7.18 (1 H, d,  $J$  = 9 Hz, Ar); 5.83 (1 H, s, CHPh); 4.58 (1H, m, CHOH); 4.31 (1H, m, indoline C(2)H); 4.21 (2 H, s,  $\underline{\text{CH}_2\text{NH}_2}$ ); 4.15 (1 H, m, indoline C(2)H); 3.18 (2 H, t,  $J$  = 8 Hz, indoline C(3)H<sub>2</sub>); 1.4 (3 H, d,  $J$  = 7 Hz, CH<sub>3</sub>).  
10   HPLC (Luna 2, Gradient 1): rt = 3.31 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.72 minutes, 473 (MH)<sup>+</sup>.

**Example 48**

15   **3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-prolinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using D-proline.

1   <sup>1</sup>H NMR ( $d_4$  MeOH): 8.41 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.48 - 7.39 (4 H, m, Ar); 7.23 (1 H, d,  $J$  = 11 Hz, Ar); 5.82 (1 H, s, CHPh); 4.63 (1 H, m, proline C(2)H); 4.24 (4 H, m,  $\text{CH}_2\text{NH}_2$  and indoline C(2)H<sub>2</sub>); 3.52-3.24 (3 H, m, indoline C(3)H<sub>2</sub> and proline C(5)H); 2.63 (1 H, m, proline C(5)H); 2.23 - 2.08 (4 H, m, proline C(3)H<sub>2</sub> and C(4)H<sub>2</sub>).  
25   HPLC (Luna 2, Gradient 1): rt = 2.98 minutes.  
HPLC (Symmetry, Gradient 2): rt = 4.87 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 498 (MH)<sup>+</sup>.

**Example 49**

30   **3-(Aminomethyl)benzoyl-D-phenylglycine 1-L-serinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using L-serine.

<sup>1</sup>H NMR ( $d_4$  MeOH) : 8.40 ppm (1 H, s, Ar); 7.95 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.47 - 7.39 (4 H, m, Ar); 7.23 (1 H, d,  $J$  = 10 Hz, Ar); 5.81 (1 H, s, CHPh); 4.4 (1 H, dd,  $J$  = 12 Hz, 4 Hz, serine CH<sub>a</sub>H<sub>b</sub>OH); 4.25 (2 H, t,  $J$  = 7 Hz, 5 indoline C(2)H<sub>2</sub>); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.05 (1 H, dd,  $J$  = 12, 6 Hz, serine CH<sub>a</sub>H<sub>b</sub>OH); 3.91 (1 H, m, serine CHNH<sub>2</sub>); 3.25 (2 H, t,  $J$  = 7 Hz, indoline C(3)H<sub>2</sub>).  
HPLC (Luna 2, Gradient 1): rt = 2.84 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 488 (MH)<sup>+</sup>.

10

**Example 50****3-(Aminomethyl)benzoyl-D-phenylglycine 1-D-serinoyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using D-serine.

15 <sup>1</sup>H NMR ( $d_4$  MeOH) : 8.42 ppm (1 H, s, Ar); 7.97 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.47 - 7.39 (4 H, m, Ar); 7.23 (1 H, d,  $J$  = 9 Hz, Ar); 5.82 (1 H, s, CHPh); 4.41 (1 H, dd,  $J$  = 12, 4 Hz, serine CH<sub>a</sub>H<sub>b</sub>OH); 4.25 (2 H, t,  $J$  = 7.5 Hz, indoline C(2)H<sub>2</sub>); 4.2 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.05 (1 H, dd,  $J$  = 12, 6 Hz, serine CH<sub>a</sub>H<sub>b</sub>OH); 3.9 (1 H, mserine CHNH<sub>2</sub>); 3.25 (2 H, t,  $J$  = 7.5 Hz, indoline C(3)H<sub>2</sub>).  
HPLC (Luna 2, Gradient 1): rt = 2.78 minutes.  
HPLC (Symmetry, Gradient 2): rt = 4.61 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 0.65 minutes, 488 (MH)<sup>+</sup>.

25

**Example 51****3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-pyridyl-acetyl)-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

30 Prepared using 3-pyridylacetic acid.

<sup>1</sup>H NMR ( $d_3$  acetonitrile): 8.91 ppm (1 H, br s, Ar), 8.73-8.55 (2 H, m, Ar), 8.35 (1 H, br s, Ar), 8.15 (1 H, d,  $J$  = 10 Hz,

Ar), 8.05-7.95 (2 H, m, Ar), 7.80 (1H, d,  $J$  = 10 Hz, Ar), 7.74 - 7.15 (10 H, m, Ar & 2 x amide NH), 5.69 (1 H, d,  $J$  = 7 Hz, CHPh), 4.25 - 4.12 (4 H, m, ArCH<sub>2</sub>N & dihydroindole C(2)H<sub>2</sub>), 3.98 (2 H, s, C(O)CH<sub>2</sub>Py), 3.17 (2 H, t,  $J$  = 8 Hz, dihydroindole C(3)H<sub>2</sub>).  
5

HPLC (Luna 2, Gradient 1): rt = 2.96 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 520 (MH<sup>+</sup>).

### Example 52

10 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(N-acetyl)-aminoacetyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using N-acetylglycine.

15 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.31 ppm (1 H, s, Ar); 7.95 (2 H, m, Ar); 7.64 - 7.57 (4 H, m, Ar); 7.43 - 7.38 (4 H, m, Ar); 7.18 (1H, d,  $J$  = 10 Hz, Ar); 5.81 (1H, s, CHPh); 4.23 - 4.11 (6 H, m, ArCH<sub>2</sub>NH<sub>2</sub>, aminoacetyl CH<sub>2</sub> and dihydroindole C(2)H<sub>2</sub>); 3.21 (2 H, t,  $J$  = 7 Hz, dihydroindole C(3)H<sub>2</sub>); 2.07 (3H, s, COCH<sub>3</sub>).

20 HPLC (Luna 2, Gradient 1): rt = 3.33 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.20 minutes.

LC/MS (Luna 2, Gradient 4): rt = 0.59 minutes, 500 (MH)<sup>+</sup>.

### Example 53

25 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(hydroxyacetyl)-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using 2-benzyloxyacetic acid.

30 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.25 ppm (1 H, s, Ar); 7.85 (2 H, m, Ar); 7.54 - 7.47 (4 H, m, Ar); 7.35 - 7.26 (4 H, m, Ar); 7.10 (1 H, d,  $J$  = 11 Hz, Ar); 4.21 (2 H, s, CH<sub>2</sub>OH); 4.10 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.95 (2 H, t,  $J$  = 7.5 Hz, dihydroindole C(2)H<sub>2</sub>);

3.21 (2 H, t,  $J$  = 7.5 Hz, dihydroindole C(3)H<sub>2</sub>) .

HPLC (Luna 2, Gradient 1): rt = 3.23 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.26 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.67 minutes, 500 (MH)<sup>+</sup>.

5

**Example 54**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-phenylacetyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using phenylacetic acid.

10 <sup>1</sup>H NMR (d<sub>3</sub>, acetonitrile): 8.78 (1 H, br s, Ar), 8.23 (1 H, br s, Ar), 7.90 (2 H, s, Ar), 7.73 (1H, d,  $J$  = 10 Hz, Ar), 7.60 - 7.01 (14 H, m, Ar & 2 x amide NH), 5.60 (1 H, d,  $J$  = 7 Hz, CHPh), 4.10 - 3.97 (4 H, m, ArCH<sub>2</sub>N & dihydroindole C(2)H<sub>2</sub>), 3.71 (2 H, s, PhCH<sub>2</sub>), 2.99 (2 H, t,  $J$  = 8 Hz, dihydroindole

15 C(3)H<sub>2</sub>) .

HPLC (Luna 2, Gradient 1): rt = 4.17 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.26 minutes, 519 (MH<sup>+</sup>) .

**Example 55**

20 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(methylamino)-acetyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using sarcosine.

25 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.39 ppm (1 H, s, indoline C(7)H); 7.95 (2 H, br s, 3-(aminomethyl)phenyl C(2)H and C(6)H); 7.72 - 7.53 (4 H, m, Ar); 7.47 - 7.31 (4 H, m, Ar); 7.24 (1 H, d,  $J$  = 10 Hz, indoline C(4)H or C(5)H); 5.82 (1 H, br s, CHPh); 4.20 (2 H, s, CH<sub>2</sub>NH<sub>2</sub> or C(O)CH<sub>2</sub>NHMe); 4.15 (2 H, s, CH<sub>2</sub>NH<sub>2</sub> or C(O)CH<sub>2</sub>NHMe); 4.10 (2 H, t,  $J$  = 9 Hz, indoline C(2)H<sub>2</sub>); 3.25 (2 H, t,  $J$  = 9 Hz, indoline C(3)H<sub>2</sub>); 2.81 (3 H, s, CH<sub>3</sub>) .

HPLC (Symmetry C8, Gradient 2): rt = 4.75 min.

LCMS (Luna 2, Gradient 4): rt = 1.45 min, 472 (MH)<sup>+</sup>.

**Example 56**

**3-(Aminomethyl)benzoyl-D-phenylglycine 3-aminopropionyl-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

5 Prepared using  $\beta$ -alanine.

$^1\text{H}$  NMR ( $\text{D}_2\text{O}$ ): 7.98 ppm (1 H, s, indoline C(7)H); 7.72 (2 H, br s, 3-(aminomethyl)phenyl C(2)H and C(6)H); 7.60 - 7.30 (7 H, m, Ar); 7.08 (1 H, d,  $J$  = 10 Hz, indoline C(4)H or C(5)H); 6.95 (1 H, d,  $J$  = 10 Hz, indoline C(4)H or C(5)H); 5.57 (1 H, s,  $\text{CHPh}$ ); 4.09 (2 H, s,  $\text{ArCH}_2\text{NH}_2$ ); 3.82 (2 H, t,  $J$  = 7 Hz, indoline C(3)H<sub>2</sub>); 3.20 (2 H, t,  $J$  = 4.5 Hz, C(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>); 2.95 (2 H, t,  $J$  = 7 Hz, indoline C(3)H<sub>2</sub>); 2.71 (2 H, t,  $J$  = 4.5 Hz, C(O)CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>).

HPLC (Symmetry C8, Gradient 2): rt = 4.80 minutes.

15 LCMS (Luna 2, Gradient 4): rt = 1.53 minutes, 472 (MH)<sup>+</sup>.

**Example 57**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(4-pyridyl-acetyl)-2,3-dihydroindol-6-amide bis-trifluoroacetate**

20 **salt**

Prepared using 4-pyridylacetic acid.

$^1\text{H}$  NMR ( $\text{CD}_3\text{CN}$ ): 8.91 (1 H, br s, Ar), 8.73-8.55 (2 H, m, Ar), 8.35 (1 H, br s, Ar), 8.15 (1 H, d,  $J$  = 10 Hz, Ar), 8.05-7.95 (2 H, m, Ar), 7.80 (1 H, d,  $J$  = 10 Hz, Ar), 7.74 - 7.15 (10 H, m, Ar & 2 x amide NH), 5.69 (1 H, d,  $J$  = 7 Hz,  $\text{CHPh}$ ), 4.25 - 4.12 (4 H, m,  $\text{PhCH}_2\text{N}$  & dihydroindole C(2)H<sub>2</sub>), 3.98 (2 H, s, C(O)CH<sub>2</sub>Py), 3.17 (2 H, t,  $J$  = 8 Hz, dihydroindole C(3)H<sub>2</sub>).

HPLC (Symmetry, Gradient 2): rt = 5.43 minutes.

30 LC/MS (Luna 2, Gradient 4): rt = 1.56 minutes, 520 (MH)<sup>+</sup>.

**Example 58**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(imidazol-4-ylacetyl)-2,3-dihydroindol-6-amide bis(trifluoroacetate) salt**

Prepared using imidazol-4-ylacetic acid.

5   <sup>1</sup>H NMR (D<sub>2</sub>O) : 7.75 ppm (1 H, br s, NH); 7.49 (2 H, br s, Ar);  
7.28 (1 H, d, J = 8 Hz, Ar); 7.24-7.12 (9 H, m, Ar); 6.92 (1 H, d, J = 8 Hz, Ar); 6.74 (1 H, d, J = 8 Hz, Ar); 6.28 (1H, s, NH); 5.38 (1 H, s, CHPh); 3.87 (2 H, s, ArCH<sub>2</sub>NH<sub>2</sub>); 3.72 (2 H, d, J = 8 Hz, dihydroindole C(2)H<sub>2</sub>); 3.52 (2 H, br s, CH<sub>2</sub>Im); 2.70 (2 H, t, J = 8 Hz, dihydroindole C(3)H<sub>2</sub>).  
10   HPLC (Symmetry, Gradient 2): rt = 4.89 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.45 minutes, 509 (MH)<sup>+</sup>.

**Example 59**

15   **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-aminothiazol-4-yl)-acetyl-2,3-dihydroindol-6-amide dihydrochloride.**

Prepared using (2-formamidothiazol-4-yl)acetic acid.

1   <sup>1</sup>H NMR (D<sub>2</sub>O) : 7.77 ppm (1 H, br s, NH); 7.51 (2 H, br s, Ar);  
20   7.29 (1 H, d, J = 8 Hz, Ar); 7.24-7.03 (9 H, m, Ar); 6.91 (1 H, d, J = 8 Hz, Ar); 6.72 (1 H, d, J = 8 Hz, Ar); 6.22 (1H, s, NH); 5.32 (1 H, s, CHPh); 3.85 (2 H, s, ArCH<sub>2</sub>NH<sub>2</sub>); 3.73 (2 H, d, J = 8 Hz, dihydroindole C(2)H<sub>2</sub>); 3.56 (2 H, br s, CH<sub>2</sub>Thz); 2.76 (2 H, t, J = 8 Hz, dihydroindole C(3)H<sub>2</sub>).  
25   HPLC (Symmetry, Gradient 2): rt = 5.03 minutes.  
LC/MS (Luna 2, Gradient 4): rt = 1.51 minutes, 541 (MH)<sup>+</sup>.

**Example 60**

30   **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-formylaminothiazol-4-yl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt**

Prepared using (2-formylaminothiazol-4-yl)acetic acid.

<sup>1</sup>H NMR (D<sub>2</sub>O) : 8.30 ppm (1 H, s, NCHO); 7.90 (1 H, br s, ArNH); 7.64 (2 H, br s, Ar); 7.42 (1 H, d, J = 8 Hz, Ar); 7.38 - 7.26 (9 H, m, Ar & NH); 7.01 (1 H, d, J = 8 Hz, Ar); 6.96 (1 H, d, J = 8 Hz, Ar); 6.82 (1H, s, NH); 5.50 (1 H, s, CHPh); 4.06 (2 H, s, ArCH<sub>2</sub>NH<sub>2</sub>); 3.90 (2 H, d, J = 8 Hz, dihydroindole C(2)H<sub>2</sub>); 3.64 (2 H, br s, CH<sub>2</sub>Thz); 2.90 (2 H, t, J = 8 Hz, dihydroindole C(3)H<sub>2</sub>).

HPLC (Symmetry, Gradient 2) : rt = 5.75 minutes.

LC/MS (Luna 2, Gradient 4) : rt = 2.10 minutes, 569 (MH)<sup>+</sup>.

10

**Example 61**

**3-(Aminomethyl)benzoyl-D/L-(4-aminomethyl)phenylglycine  
indan-5-amide bis(trifluoroacetate) salt.**

15   **Methyl 4-bromophenylacetate**

Thionyl chloride (18 mL, 0.25 mol) was added dropwise to a solution of 4-bromo-phenylacetic acid (50 g; 0.23 mol) in methanol (250 mL). The resulting mixture was stirred at room temperature for 1 hour before the methanol was removed *in vacuo*. Ethyl acetate (300 mL) was added and the resulting solution was washed with water (3 x 150 mL) and 1M aqueous NaHCO<sub>3</sub> (1 x 150 mL), dried (MgSO<sub>4</sub>) and evaporated to give the ester (52.8 g; 100 %) as an orange oil which was used without further purification.

25   <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 7.38 ppm (2 H, d, J = 8.4 Hz, C(2)H and C(6)H); 7.09 (2 H, d, J = 8.4 Hz, C(3)H and C(5)H); 3.63 (3 H, s, OMe); 3.51 (2 H, s, CH<sub>2</sub>).

**Methyl 4-cyanophenylacetate**

30   Zinc cyanide (10.4 g, 0.088 mol) and tetrakis-(triphenylphosphine)palladium(0) (5 g, 4.4 mmol) were added to a solution of methyl 4-bromophenylacetate (20 g, 0.088

mol) in dimethylformamide (150 mL). The resulting mixture was stirred at 80°C for 5 hours, then allowed to cool to room temperature. Toluene (500 mL) and 1M aqueous ammonia (500 mL) were added, the layers were separated and the 5 organic layer washed with brine (100 mL) and dried ( $\text{MgSO}_4$ ). Evaporation of the solvents afforded an off-white solid, which was purified by silica gel chromatography to afford the cyano-compound as a white solid (11.3 g; 73 %).

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.65 ppm (2 H, d,  $J = 8.4$  Hz, C(3)H and C(5)H); 7.42 (2 H, d,  $J = 8.1$  Hz, C(2)H and C(6)H); 3.74 (3H, s, OMe); 3.72 (2H, s,  $\text{CH}_2$ ).

#### **4-Cyanophenylacetic acid**

A solution of methyl 4-cyanophenylacetate (23.9 g; 0.136 mol) in ethanol (250 mL) was stirred at room temperature and a solution of sodium hydroxide (6.0 g; 0.15 mol) in water (25 mL) was added. After 2 hours the ethanol was removed *in vacuo*. Ethyl acetate (300 mL) and 5% aqueous HCl (300 mL) were added and the layers were separated. The aqueous layer 15 was extracted with ethyl acetate (300 mL) and the combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to give the acid (21.6 g; 99 %) which was used without further purification.

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.57 ppm (2 H, d,  $J = 8.3$  Hz, C(3)H and C(5)H); 7.34 (2 H, d,  $J = 8.2$  Hz, C(2)H and C(6)H); 3.64 (2 H, s,  $\text{CH}_2$ ).

#### **4-(N-BOC-aminomethyl)phenylacetic acid**

A solution of 4-cyanophenylacetic acid (12.11 g, 0.075 mol) 25 in water (163 mL) and concentrated aqueous ammonia (40 mL) was stirred at room temperature and Raney nickel (6.3 g) was added. The resulting suspension was stirred under a

hydrogen atmosphere for 24 hours before the reaction mixture was filtered through celite and evaporated *in vacuo* to give crude 4-(aminomethyl)-phenylacetic acid (12.57 g; 100 %) as a pale blue solid.

5 A solution of the crude amino acid (12.57 g, 0.075 mol) in water (50 mL) and 1,4-dioxane (50 mL) was stirred at room temperature and sodium hydroxide (3 g, 0.075 mol) and di-<sup>t</sup>butyl dicarbonate (16.4 g, 0.075 mol) were added simultaneously. After 24 hours the 1,4-dioxane was removed  
10 *in vacuo* and the aqueous layer was acidified with saturated aqueous citric acid (200 mL). The solution was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were dried ( $\text{MgSO}_4$ ) and evaporated *in vacuo* to give the N-BOC-amine (17.6 g, 88 %) as a white solid which was  
15 used without further purification.

<sup>1</sup>H NMR ( $\text{CDCl}_3$ ): 7.00 ppm (4 H, m, Ar); 4.65 (1 H, br s, N-H); 4.09 (2 H, d,  $J = 6$  Hz,  $\text{CH}_2\text{NH}$ ); 3.43 (2H, s,  $\text{CH}_2$ ); 1.25 (9H, s, <sup>t</sup>Bu).

20 **Methyl 4-(N-BOC-aminomethyl)phenylacetate**

1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (34.8 g, 0.18 mol) and 4-(*N,N*-dimethylamino)pyridine (220 mg, 1.8 mmol) were added to a solution of 4-(N-BOC-aminomethyl)phenylacetic acid (47.8 g, 0.18 mol) in methanol (200 ml). After stirring for 18 hours  
25 the methanol was removed *in vacuo* and the reaction mixture partitioned between ethyl acetate (200 mL) and saturated aqueous citric acid (200 mL). The organic phase was separated and washed with saturated aqueous  $\text{NaHCO}_3$  (200 mL)  
30 and brine (200 mL), dried ( $\text{MgSO}_4$ ) and evaporated to give the methyl ester (49.8 g; 99 %).

<sup>1</sup>H NMR ( $\text{CDCl}_3$ ): 7.42 ppm (4 H, s, Ar); 5.02 (1 H, br s, N-H);

4.48 (2 H, d,  $J = 5.7$  Hz,  $\text{CH}_2\text{NH}$ ) ; 3.87 (3 H, s, OMe) ; 3.79 (2 H, s,  $\text{CH}_2$ ) ; 1.64 (9 H, s,  $^t\text{Bu}$ ) .

**Methyl [4-(N-BOC-aminomethyl)phenyl]- $\alpha$ -azidoacetate**

5 A solution of methyl 4-(N-BOC-aminomethyl)phenylacetate (9.34 g; 0.033 mol) in THF (100 mL) was stirred under argon at -78°C and potassium bis(trimethylsilyl)amide (16.7 g, 0.084 mol) in THF (50 mL) was added. After stirring for 30 minutes, 2,4,6-triisopropylbenzene-sulfonyl azide (31.1 g, 0.101 mol) was added as a solid. After 5 minutes, acetic acid (10 mL, 0.175 mol) was added and the reaction warmed to room temperature. The reaction mixture was then partitioned between ethyl acetate (500 mL) and water (500 mL), separated and the organic layer dried ( $\text{MgSO}_4$ ). Evaporation of the solvent and purification of the residue by silica gel chromatography afforded the azide (7.1 g, 67 %).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 7.28 ppm (4 H, s, Ar) ; 4.92 (1 H, s,  $\text{CHN}_3$ ) ; 4.25 (2 H, s,  $\text{CH}_2\text{NH}$ ) ; 3.69 (3 H, s, OMe) ; 1.38 (9 H, s,  $^t\text{Bu}$ ) .

20 **Methyl  $\alpha$ -amino-[4-(N-BOC-aminomethyl)phenylacetate**

A solution of methyl [4-(N-BOC-aminomethyl)phenyl]- $\alpha$ -azidoacetate (7.1 g, 0.022 mol) in ethyl acetate (50 mL) was stirred over palladium on carbon (5%). The reaction vessel was taken up to 250 psi with hydrogen for 17 hours. The reaction mixture was filtered through celite and evaporated *in vacuo* to give the amine (6.47 g, 100 %) as a pale solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 7.20 ppm (2 H, m, Ar) ; 7.12 (2 H, m, Ar) ; 4.81 (1 H, br s, NH) ; 4.45 (1 H, s, CH) ; 4.18 (2 H, d,  $J = 6$  Hz,  $\text{CH}_2\text{NH}$ ) ; 3.54 (3 H, s, OMe) ; 2.09 (2 H, br s,  $\text{NH}_2$ ) ; 1.30 (9 H, s,  $^t\text{Bu}$ ) .

**Methyl  $\alpha$ -(N-benzyloxycarbonyl-amino)-[4-(N-BOC-**

**aminomethyl)phenyl]acetate**

A solution of the amine (530 mg, 1.8 mmol) in tetrahydrofuran (15 mL) was treated with triethylamine (0.25 mL, 1.8 mmol) and benzyl chloroformate (0.26 mL, 1.8 mmol) and allowed to stir at room temperature for 1 hour. The reaction was diluted with ethyl acetate (40 mL), washed with brine (2 x 25 mL), dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford a yellow oil. The benzyloxycarbonyl ester was purified by flash chromatography 10 on silica gel (ethyl acetate / hexane 1 : 1) to give a yellow solid (312 mg, 66 %).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.32 - 7.15 ppm (9 H, m, 9 Ar); 5.80 (1 H, br s, NH); 5.30 (1 H, d,  $J = 9.6$  Hz, CH); 5.01 (2 H, s,  $\text{CH}_2\text{Ph}$ ); 4.22 (2 H, d,  $J = 7.2$  Hz,  $\text{CH}_2\text{NHBOC}$ ); 3.63 (3 H, s, OCH<sub>3</sub>); 15 1.39 (9 H, s,  $^t\text{Bu}$ ).

**D/L- $\alpha$ - (N-benzyloxycarbonyl) - [4- (N-BOC- aminomethyl) phenyl]glycine**

A solution of the ester (356 mg, 0.83 mmol) in tetrahydrofuran (15 mL) was treated with 1 M LiOH (1.7 mL, 1.7 mmol) and heated at reflux for 3 hours. The solvent was removed under reduced pressure and the residue diluted with water (20 mL). The pH was reduced to 4 using 5 % aqueous HCl and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to afford the acid as a yellow solid (273 mg, 79 %) which was carried forward without further purification.

30 **D/L- $\alpha$ - (N-benzyloxycarbonyl) - [4- (N-BOC- aminomethyl)phenyl]glycine indan-5-amide.**

A solution of the acid (173 mg, 0.42 mmol) in

dimethylformamide (15 ml) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg, 0.42 mmol), 1-hydroxy-7-azabenzotriazole (57 mg, 0.42 mmol), 5-aminoindane (56 mg, 0.42 mmol) and 4-(*N,N*-dimethylamino)pyridine (5 mg) and stirred overnight at room temperature before being partitioned between ethyl acetate (50 mL) and water (50 mL). The layers were separated and the organic phase was washed with 5 % aqueous HCl (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and water (25 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford the indanamide as a colourless solid (160 mg, 72 %) which was used without further purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.39 - 7.09 ppm (12 H, m, 10 Ar and 2 NH); 6.99 (2 H, s, Ar); 5.38 (1 H, br s, CHAr); 5.01 (2 H, s, CH<sub>2</sub>Ph); 4.81 (1 H, m, NH); 4.19 (2 H, s, CH<sub>2</sub>NHBOC); 2.85 - 2.68 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.04 - 1.88 (2 H, m, indane C(2)H<sub>2</sub>); 1.39 (9 H, s, <sup>t</sup>Bu).

**3-(N-BOC-Aminomethyl)benzoyl-D/L-4-(N-BOC-aminomethyl)-phenylglycine indan-5-amide**

10 % Palladium on carbon (50 mg), was added to a solution of the indanamide (160 mg, 0.3 mmol) in ethanol (20 mL) and the suspension was stirred under a hydrogen atmosphere overnight. The mixture was filtered and the filter was washed with ethanol (20 ml). The combined filtrates were concentrated under reduced pressure to afford the amine as a colourless solid (107 mg, 90 %) which was carried forward without further purification.

A solution of the amine (107 mg, 0.27 mmol) in dimethylformamide (15 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (52 mg, 0.27 mmol), 1-hydroxy-7-azabenzotriazole (37 mg, 0.27

mmol), *N*-BOC-3-(aminomethyl)benzoic acid (68 mg, 0.27 mmol) and 4-(*N,N*-dimethylamino)pyridine (5 mg) and stirred overnight at room temperature. The solution was partitioned between ethyl acetate (25 mL) and water (25 mL) and the  
5 organic phase was separated and washed with 5 % aqueous HCl (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and water (25 mL) before being dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford a yellow solid. The residue was purified by flash chromatography on silica gel (ethyl acetate /  
10 hexane 1 : 1) to give the diprotected bis-amide as a colourless solid (103 mg, 61 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 9.25 ppm (1 H, s, NH); 7.94 (1 H, d, *J* = 7.2 Hz, Ar); 7.62 (2 H, s, Ar); 7.43 - 7.24 (5 H, m, 4 Ar, NH); 7.05 (3 H, d, *J* = 7.2 Hz, Ar); 6.94 (1 H, d, *J* = 7.2 Hz, Ar); 6.14 (1 H, d, *J* = 7.2 Hz, CH); 5.07 (1 H, m, NH); 4.99 (1 H, m, NH); 4.16 (2 H, s, CH<sub>2</sub>NHBOC); 4.10 (2 H, s, CH<sub>2</sub>NHBOC); 2.77 - 2.61 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 1.98 - 1.87 (2 H, m, indane C(2)H<sub>2</sub>); 1.35 (9 H, s, <sup>t</sup>Bu).

20 **3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine  
indan-5-amide bis(trifluoroacetate) salt.**

A solution of the diprotected bis-amide (103 mg, 0.16 mmol) in dichloromethane (5 mL) was stirred at room temperature and trifluoroacetic acid (3 mL) was added. Stirring was  
25 continued for a further hour before the solvents were removed under reduced pressure to afford the bis(trifluoroacetate) salt as a colourless solid (92 mg, 88 %).

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.90 ppm (1 H, s, Ar); 7.84 (1 H, s, Ar);  
30 7.65 - 7.54 (4 H, m, Ar); 7.49 - 7.32 (3 H, m, Ar); 7.12 (1 H, d, *J* = 7.2 Hz, Ar); 7.02 (1 H, d, *J* = 7.2 Hz, Ar); 5.78 (1 H, s, CHAr); 4.08 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 4.01 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>);

2.79 - 2.70 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>) ; 2.03 - 1.90 (2 H, m, indane C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 3.13 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.45 minutes, 429 (MH)<sup>+</sup>.

5

Examples 62 - 64 were prepared in a similar fashion to Example 61, using the specified amine in place of 5-aminoindane.

10 **Example 62**

**3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine  
1-aminoacetyl-2,3-dihydroindol-6-amide  
tris(trifluoroacetate salt)**

Prepared from 6-amino-1-(N-BOC-aminoacetyl)-2,3-dihydroindole.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.23 ppm (1 H, s, Ar) ; 7.84 - 7.74 (2 H, m, Ar) ; 7.56 - 7.30 (6 H, m, Ar) ; 7.17 (1 H, d, J = 7.2 Hz, Ar) ; 7.02 (1 H, d, J = 7.2 Hz, Ar) ; 5.68 (1 H, s, CHAr) ; 4.02 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 3.99 - 3.79 (6 H, m, CH<sub>2</sub>NH<sub>2</sub>, dihydroindole C(2)H<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub> glycine) ; 3.06 - 2.97 (2 H, m, dihydroindole C(3)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.13 minutes.

LCMS (Luna 2, Gradient 4): rt = 0.51 minutes, 487 (MH)<sup>+</sup>.

25 **Example 63**

**3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine 1-acetyl-2,3-dihydroindole bis(trifluoroacetate) salt**

Prepared from 1-acetyl-6-amino-2,3-dihydroindole.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.21 ppm (1 H, s, Ar) ; 7.97 - 7.86 (2 H, m, Ar) ; 7.72 - 7.43 (6 H, m, Ar) ; 7.32 (1 H, d, J = 7.2 Hz, Ar) ; 7.12 (1 H, d, J = 7.2 Hz, Ar) ; 5.81 (1 H, s, CHAr) ; 4.17 (1 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 4.15 - 4.04 (4 H, m, CH<sub>2</sub>NH<sub>2</sub>,

dihydroindole C(2)H<sub>2</sub>) ; 3.19 - 3.07 (2 H, m, dihydroindole C(3)H<sub>2</sub>) ; 2.20 (3 H, s, NCOCH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 2.72 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.18 minutes, 472 (MH)<sup>+</sup>.

5

**Example 64**

**3-(Aminomethyl)benzoyl-D/L-4-(aminomethyl)phenylglycine  
4-(isopropyl)phenylamide bis(trifluoroacetate salt)**

Prepared from 4-isopropylaniline.

10 <sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.01 - 7.92 ppm (2 H, m, Ar) ; 7.75 - 7.43 (8 H, m, Ar) ; 7.18 (2 H, d, J = 9.6 Hz, Ar) ; 5.87 (1 H, s, CHAr) ; 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 4.14 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 2.96 - 2.81 (1 H, m, CH(CH<sub>3</sub>)<sub>2</sub>) ; 1.24 (6 H, d, J = 7 Hz, CH(CH<sub>3</sub>)<sub>2</sub>) .  
HPLC (Luna 2, Gradient 1): rt = 3.39 minutes.

15 LCMS (Luna 2, Gradient 4): rt = 1.59 minutes, 431 (MH)<sup>+</sup>.

Examples 65 - 68 were prepared in a similar manner to Example 61 except that the indicated protected amino acid was used in the place of D/L-4-(N-BOC-aminomethyl)-α-(N-benzyloxycarbonyl)phenylglycine.

**Example 65**

**3-(Aminomethyl)benzoyl-D-cyclohexylglycine indan-5-amide  
trifluoroacetate salt**

25 Prepared from N-BOC-D-cyclohexylglycine.

1H NMR (d<sub>4</sub> MeOH) : 7.88 - 7.02 ppm (7 H, m, Ar) ; 4.43 (1 H, d, J = 9 Hz, CH(cHex)) ; 4.04 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>) ; 2.78 - 2.68 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>) ; 2.04 - 1.82 (4 H, m, indane C(2)H<sub>2</sub>, cHex CH<sub>2</sub>) ; 1.77 - 1.56 (4 H, m, 2 x cHex CH<sub>2</sub>) ; 1.36 - 30 0.95 (5 H, m, 2 x cHex CH<sub>2</sub> and CH) .  
HPLC (Luna 2, Gradient 1): rt = 4.27 minutes.

LCMS (Luna 2, Gradient 4): rt = 2.21 minutes, 406 (MH)<sup>+</sup>.

**Example 66**

**3-(Aminomethyl)benzoyl-D/L-1-naphthylglycine indan-5-amide trifluoroacetate salt**

5 Prepared from *N*-BOC-D/L-1-naphthylglycine.

$^1\text{H}$  NMR ( $d_4$  MeOH): 8.25 ppm (1 H, d,  $J$  = 7.2 Hz, Ar); 8.04 - 7.84 (4 H, m Ar); 7.75 - 7.44 (7 H, m, Ar); 7.33 (1 H, d,  $J$  = 7.25 Hz, Ar); 7.16 (1 H, d,  $J$  = 7.25 Hz, Ar); 6.72 (1 H, s, CHAr); 4.15 (2 H, s,  $\text{CH}_2\text{NH}_2$ ); 2.94 - 2.78 (4 H, m, indane C(1)H<sub>2</sub> C(3)H<sub>2</sub>); 2.17 - 1.98 (2 H, m, indane C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.37 minutes.

LCMS (Luna 2, Gradient 4): rt = 2.37 minutes, 450 (MH)<sup>+</sup>.

**Example 67**

15 **3-(Aminomethyl)benzoyl-D/L-(4-phenyl)phenylglycine indan-5-amide trifluoroacetate salt**

Prepared from *N*-Fmoc-D/L-(4-phenyl)phenylglycine.

$^1\text{H}$  NMR ( $d_4$  MeOH): 7.94 - 7.83 ppm (2 H, m, Ar); 7.64 - 7.15 (13 H, m, Ar); 7.02 (1 H, d,  $J$  = 7.2 Hz, Ar); 5.80 (1 H, s, CH); 4.08 (2 H, s,  $\text{CH}_2\text{NH}_2$ ); 2.81 - 2.77 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.01 - 1.88 (2 H, m, indane C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.87 minutes.

LCMS (Luna 2, Gradient 4): rt = 2.56 minutes, 476 (MH)<sup>+</sup>.

**Example 68**

25 **3-(Aminomethyl)benzoyl-D-(4-aminophenyl)glycine indan-5-amide bis(trifluoroacetate) salt**

Prepared from *N*-BOC-D-(4-Benzyloxycarbonylaminophenyl)-glycine (prepared as described below).

30 **D-(4-Hydroxyphenyl)glycine methyl ester hydrochloride**  
**D-4-Hydroxyphenylglycine (12.5 g, 74.8 mmol) and dry**

methanol (24 mL) were stirred in a dry 250 mL three necked round bottom flask, equipped with a low temperature thermometer. The mixture was stirred under nitrogen and cooled to an internal temperature of below -20°C. Using a 5 syringe, thionyl chloride (6 mL, 9.78 g, 82.2 mmol) was added dropwise to the cooled mixture over a period of 10 minutes at such a rate that the internal temperature did not exceed -20°C. Once the addition was complete the mixture was allowed to warm to room temperature and stirred 10 overnight. Dry ether (150 mL) was added and the white precipitate that formed was collected by suction filtration, washed with a little more ether and dried (15.5g, 95%).

**N-BOC-D- (4-Hydroxyphenyl)glycine methyl ester**

15 Di-t-butyl dicarbonate (15.9 g, 72.8 mmol) was added to a stirred mixture of D-4-hydroxyphenylglycine methyl ester hydrochloride (14 g, 64.3 mmol) and NaHCO<sub>3</sub> (11.7 g, 0.14 mol) in tetrahydrofuran (150 mL) and water (50 mL), in one portion. The mixture was stirred rapidly for 4h. Hexane 20 (75 mL) was added and the organic layer separated and washed with saturated aqueous NaHCO<sub>3</sub> (20 mL) and brine (20 mL) and dried (MgSO<sub>4</sub>). Evaporation of the solvent afforded the N-BOC-protected amine (19.7g, 96%).

25 **N-BOC-D- (4-Trifluoromethylsulphonyloxyphenyl)glycine methyl ester**

2,6-Lutidine (9.44 ml, 8.68 g, 81.0 mmol) and 4-dimethylaminopyridine (1.65 g, 13.5 mmol) were added to a stirred solution of *N*-BOC-D- (4-hydroxyphenyl)glycine methyl ester (19 g, 67.5 mmol) in dichloromethane (400 mL) and the mixture cooled in an ice bath. Trifluoromethanesulphonic anhydride (13.7 mL, 23.0 g, 81.4 mmol) was added over a

period of five minutes and then the mixture was allowed to warm to room temperature over four hours. The solution was washed with water (2 x 150 mL), 1N HCl (2 x 150 mL) and saturated aqueous NaHCO<sub>3</sub> (150 mL) and dried (MgSO<sub>4</sub>).

5 Evaporation of the solvent afforded an oil which was purified by flash chromatography on silica gel (hexane / dichloromethane 1:1 and then neat dichloromethane) affording the triflate as a white solid (19 g, 77%).

10 **N-BOC-D- (4-benzyloxycarbonylphenyl)glycine methyl ester**

N-BOC-D- (4-trifluoromethylsulphonyloxyphenyl)glycine methyl ester (27.6 g, 77.0 mmol), benzyl alcohol (32.6 mL, 34.1 g, 315 mmol), palladium (II) acetate (255 mg, 1.13 mmol), bis-1,3-diphenylphosphinylpropane (448 mg, 1.09 mmol) and triethylamine (10.2 mL, 7.40 g, 73.2 mmol) in dimethylformamide (72 mL) were placed in a Parr reactor and the reactor assembled. The vessel was pressurised to ~10 psi with nitrogen and the gas released (repeated five times to remove all oxygen from the system). Carbon monoxide gas was then carefully introduced to ~20 psi and released three times. Carbon monoxide was then added to ~100 psi and the stirrer started. The vessel was slowly heated to 65 °C internal temperature and then stirred, monitoring by tlc. When complete (after ~ 18 hours) the reaction was cooled to 30°C, the gas released and the vessel flushed five times with nitrogen as before. The reaction mixture was partitioned between ethyl acetate (250 mL) and water (100 mL) and the organic layer washed with 1M hydrochloric acid (30 mL) and saturated aqueous NaHCO<sub>3</sub> (30 mL) and dried (MgSO<sub>4</sub>) and evaporated. Purification of the resulting oil by column chromatography (ethyl acetate / hexane; 1:4) gave the benzyl ester (18.7 g, 70%).

**N-BOC-D- (4-hydroxycarbonylphenyl)glycine methyl ester**

10 % Palladium on carbon (100 mg) was added to a solution of the benzyl ester (500 mg, 1.25 mmol) in ethanol (15 mL) and 5 the suspension was stirred under a hydrogen atmosphere overnight. The mixture was filtered and the residue was washed with ethanol (20 mL) and the combined organic solvents were evaporated under reduced pressure to afford the acid as a colourless solid (363 mg, 94 %).

10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 8.08 ppm (2 H, br s, Ar); 7.49 (2 H, d,  $J$  = 7.2 Hz, Ar); 5.87 (1 H, d,  $J$  = 9 Hz, NHCH); 3.73 (3 H, s, OCH<sub>3</sub>); 1.41 (9 H, s, <sup>t</sup>Bu).

**N-BOC-D- (4-Benzylloxycarbonylaminophenyl)glycine methyl ester.**

15 The acid (218 mg, 0.7 mmol) in tetrahydrofuran (20 mL) was treated with triethylamine (108  $\mu\text{l}$ , 0.78 mmol) and diphenylphosphonic azide (161  $\mu\text{l}$ , 0.78 mmol) and stirred at room temperature for 1.5 hours. Benzyl alcohol (116  $\mu\text{l}$ , 20 1.12 mmol) was then added and the mixture was heated at reflux for 18 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (ethyl acetate / hexane, 1:1) to give the *N*-benzylloxycarbonylaniline as a brown solid (87 mg, 30 %).

25  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.35 - 7.23 ppm (7 H, m, Ar); 7.16 (2 H, d,  $J$  = 9 Hz, Ar); 7.06 (1 H, s, NH); 5.53 (1 H, d,  $J$  = 9 Hz, CHAr); 5.18 (1 H, d,  $J$  = 9 Hz, NH); 5.10 (2 H, s, CH<sub>2</sub>Ph); 3.59 (3 H, s, OCH<sub>3</sub>); 1.31 (9 H, s, <sup>t</sup>Bu).

**30 *N*-BOC-D- (4-Benzylloxycarbonylaminophenyl)glycine**

A solution of the ester (87 mg, 0.21 mmol) in tetrahydrofuran (5 mL) was treated with 1 M LiOH (0.84 ml,

0.84 mmol) and heated at reflux for four hours. The solvent was removed under reduced pressure and the residue was diluted with water (10 mL). The aqueous solution was acidified to pH 4 using 5 % aqueous HCl and extracted with 5 ethyl acetate (3 x 10 mL). The combined extracts were dried ( $\text{MgSO}_4$ ) and evaporated under reduced pressure to afford the crude acid (80 mg, 95 %) as a colourless solid which was carried forward without further purification.

10 **3-(Aminomethyl)benzoyl-D-(4-aminophenyl)glycine indan-5-amide bis(trifluoroacetate) salt.**

$^1\text{H}$  NMR ( $d_4$  MeOH): 7.92 - 7.80 ppm (2 H, m, Ar); 7.69 (2 H, d,  $J$  = 7.3 Hz, Ar); 7.60 - 7.40 (2 H, m, Ar); 7.34 (3 H, d,  $J$  = 12 Hz, Ar); 7.15 (1 H, d,  $J$  = 7.2 Hz, Ar); 7.02 (1 H, d,  $J$  = 7.2 Hz, Ar); 5.79 (1 H, s, CHAr); 4.07 (2 H, s,  $\text{CH}_2\text{NH}_2$ ); 2.80 - 2.69 (4 H, m, indane C(1) $\text{H}_2$  and C(3) $\text{H}_2$ ); 2.01 - 1.88 (2 H, m, indane C(2) $\text{H}_2$ ).

HPLC (Luna 2, Gradient 1): rt = 3.17 minutes.

LCMS (Luna 2, Gradient 4): rt = 1.59 minutes, 415 ( $\text{MH}^+$ ).

20

**Example 69**

**3-(Aminomethyl)benzoyl-D/L-piperidin-4-ylglycine indan-5-amide bis(trifluoroacetate) salt**

25 **(N-BOC-Piperidin-4-ylidene)- (N-benzyloxycarbonyl)glycine methyl ester**

$N$ -BOC-4-Piperidone (2.0 g, 10 mmol),  $N$ -(benzyloxy-carbonyl)- $\alpha$ -phosphonoglycine trimethyl ester (3.64 g, 2.20 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.57 mL, 2.10 mmol) were 30 stirred in acetonitrile overnight. The solvent was removed and the residue taken up in ethyl acetate (50 mL) and washed with water (2 x 10 mL), dried ( $\text{MgSO}_4$ ) and evaporated under

reduced pressure. The residual oil was purified by chromatography on silica gel (ethyl acetate / hexane, 40 % / 60 %) to afford the unsaturated ester (3.63 g, 90 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.36 ppm (5 H, br s, Ph); 6.05 (1 H, br s, NH); 5.12 (2 H, s, CH<sub>2</sub>Ph); 3.73 (3 H, br s, OMe); 3.50 (4 H, br s, piperidine C(2)H<sub>2</sub> and C(6)H<sub>2</sub>); 2.86 (2 H, br s, piperidine C(3) H<sub>2</sub> or C(5) H<sub>2</sub>); 2.45 - 2.36 (2 H, m, piperidine C(3) H<sub>2</sub> or C(5) H<sub>2</sub>); 1.47 (9 H, s, <sup>t</sup>Bu).

10 **(N-BOC-Piperidin-4-ylidene) - (N-benzyloxycarbonyl)glycine**

A solution of the methyl ester (391 mg, 1 mmol) in tetrahydrofuran (10 mL) was treated with 1 M LiOH (2 mL, 2 mmol) and heated at reflux for 4 hours. The solvent was removed under reduced pressure and the residue diluted with water (20 mL). The aqueous solution was acidified to pH 4 with 5 % aqueous HCl and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford the acid as a brown solid (305 mg, 78 %) which was carried forward without further purification.

15 **(N-BOC-Piperidin-4-ylidene) - (N-benzyloxycarbonyl)glycine  
indan-5-amide**

A solution of the acid (253 mg, 0.65 mmol) in 20 dimethylformamide (20 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (124 mg, 0.65 mmol), 1-hydroxy-7-azabenzotriazole (88 mg, 0.65 mmol), 5-aminoindane (86 mg, 0.65 mmol) and 4-(*N,N*-dimethylamino)pyridine (10 mg) and stirred overnight at room 25 temperature. The solution was partitioned between ethyl acetate (30 mL) and water (30 mL), separated, and the organic phase was washed with 5 % aqueous HCl (30 mL),

saturated aqueous NaHCO<sub>3</sub> (30 mL) and water (30 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford a colourless solid. The crude product was purified by flash chromatography (ethyl acetate / hexane 1 : 1) to afford the  
5 indanamide as a colourless solid (215 mg, 65 %).

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.31 (1 H, br s, NH); 7.43 (9 H, m, 8 Ar, NH); 5.01 (2 H, s, CH<sub>2</sub>Ph); 3.34 (4 H, br s, piperidine C(2)H<sub>2</sub> and C(6)H<sub>2</sub>); 2.83 - 2.71 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.54 (2 H, br s, piperidine C(3)H<sub>2</sub> or C(5)H<sub>2</sub>); 2.23 - 2.14 (2  
10 H, m, piperidine C(3)H<sub>2</sub> or C(5)H<sub>2</sub>); 2.05 - 1.92 (2 H, m, indane C(2)H<sub>2</sub>); 1.38 (9 H, s, <sup>t</sup>Bu).

**D/L-(N-BOC-Piperidin-4-yl)glycine indan-5-amide**

10 % Palladium on carbon (50 mg) was added to a solution of  
15 the alkene (215 mg, 0.43 mmol) in ethanol (20 mL) and the suspension was stirred under a hydrogen atmosphere overnight. The mixture was filtered and the filtrand was washed with ethanol (20 ml) before the combined solvents were concentrated under reduced pressure to afford the  
20 deprotected saturated amine as a colourless oil (97 mg, 60 %). The crude amine was carried forward without further purification.

The remaining steps of the synthesis are identical to those  
25 of Example 61.

**3-(Aminomethyl)benzoyl-D/L-piperidin-4-ylglycine indan-5-amide bis(trifluoroacetate) salt.**

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.04 - 7.92 ppm (2 H, m, Ar); 7.73 - 7.55  
30 (2 H, m, Ar); 7.49 (1 H, s, Ar); 7.32 (1 H, d, J = 7.2 Hz,  
Ar); 7.18 (1 H, d, J = 7.2 Hz, Ar); 4.68 (1 H, d, J = 9 Hz,  
CH(Pip)); 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.54 - 3.40 (2 H, m,

piperidine C(2)H and C(6)H); 3.13 - 2.96 (2 H, m, piperidine C(2)H and C(6)H); 2.94 - 2.81 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.41 - 2.23 (1 H, m, piperidine C(4)H); 2.20 - 1.95 (4 H, m, indane C(2)H<sub>2</sub>, piperidine C(3)H and C(4)H); 1.84 - 5 1.60 (2 H, m, piperidine C(3)H and C(4)H).  
HPLC (Luna 2, Gradient 1): rt = 3.08 minutes.  
LCMS (Luna 2, Gradient 4): rt = 1.27 minutes, 407 (MH)<sup>+</sup>.

**Example 70**

10 **2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide bis(trifluoroacetate) salt**

**2-Amino-5-cyanobenzoic acid**

A solution of 2-amino-5-bromobenzoic acid (6.9 g, 31.9 mmol) 15 in N-methyl-2-pyrrolidinone (100 mL) was treated with copper cyanide (4.14 g, 46 mmol) and the mixture was heated at 190°C for 4.5 hours before being cooled to room temperature and allowed to stand overnight. The mixture was diluted with water (500 mL), acidified with 6N aqueous HCl (100 mL) 20 and extracted with ethyl acetate (6 x 40 mL). The organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to yield the crude nitrile (4.35 g, 84 %).

**2-Amino-5-cyanobenzoyl-D-phenylglycine methyl ester**

25 A solution of 2-amino-5-cyanobenzoic acid (1.0 g, 6.17 mmol) in dimethylformamide (50 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g, 6.17 mmol) and 1-hydroxy-7-azabenzotriazole (0.84 g, 6.17 mmol). After stirring for 10 minutes, D-phenylglycine methyl 30 ester (1.24 g, 6.17 mmol) was added and the resulting solution was stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (50 mL) and

water (50 mL) and the organic solution was washed with saturated aqueous citric acid (50 mL), saturated aqueous NaHCO<sub>3</sub> (50 mL) and water (50 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude product was 5 purified by flash column chromatography (ethyl acetate / hexane, 1:1) to yield 2-amino-5-cyanobenzoyl-D-phenylglycine methyl ester (1.3 g, 68 %).

LC/MS (Luna 2, Gradient 4): rt = 3.28 minutes, 310 (MH)<sup>+</sup>.

10 **2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine methyl ester**

A solution of 2-amino-5-cyanobenzoyl-D-phenylglycine methyl ester (800 mg, 2.6 mmol) in dimethylformamide (20 mL) was treated with 4-dimethylaminopyridine (30 mg; 0.3 mmol), 1-15 (3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (500 mg; 2.6 mmol) and di-t-butyldicarbonate (570 mg; 2.6 mmol). The mixture was stirred overnight at room temperature and then partitioned between ethyl acetate (25 mL) and water (25 mL). The organic extracts were dried (MgSO<sub>4</sub>), concentrated under reduced pressure and the residue was purified by flash column chromatography (ethyl acetate / hexane 3:7) to yield the bis-protected amine (150 mg, 11 %).

20 **2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine**

25 The ester (150 mg, 0.29 mmol) was dissolved in tetrahydrofuran (20 mL) and treated with 1 M lithium hydroxide (0.6 mL, 0.6 mmol). The mixture was heated at reflux for 3 hours, cooled to room temperature and concentrated under reduced pressure. The residue was diluted 30 with water (10 mL), acidified with 5% aqueous HCl (10 mL) and the product extracted into ethyl acetate (25 mL). The organic extracts were then dried (MgSO<sub>4</sub>) and concentrated

under reduced pressure and the crude acid (110 mg, 75 %) was carried forward without further purification.

**2-(Di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine**

**5 indan-5-ylamide**

A solution of the acid (110 mg, 0.20 mmol) in dimethylformamide (10 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (30 mg, 0.2 mmol) and 1-hydroxy-7-azabeno-triazole (30 mg, 0.2 mmol). After stirring for 10 minutes, 5-aminoindane (30 mg, 0.2 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and water (25 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate / hexane, 3:7) to yield 2-(di-t-butoxycarbonyl)amino-5-cyanobenzoyl-D-phenylglycine indan-5-ylamide as an off-white solid (50 mg, 40 %).

**2-Amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide bis(trifluoroacetate) salt.**

A solution of the nitrile (50 mg, 0.08 mmol) in methanol (10 mL) and 36% aqueous HCl (0.5 mL) was stirred over 10% palladium on carbon (20 mg) under a hydrogen atmosphere for 16 hours. The mixture was filtered and the residue was washed with methanol (10 mL) before concentrating the extracts under reduced pressure.

The residue was dissolved in a mixture of trifluoroacetic acid (5 ml) and dichloromethane (5 ml) and stirred for one hour. The mixture was concentrated under reduced pressure

and the residue purified by preparative HPLC to afford 2-amino-5-(aminomethyl)benzoyl-D-phenylglycine indan-5-ylamide ditrifluoroacetate salt (2 mg, 6%).

<sup>1</sup>H NMR ( $d_4$  MeOH): 7.98-7.37 ppm (10 H, m, Ar); 7.02 (1H, d,  $J$  = 7.5 Hz, Ar); 6.03 (1H, s, CHPh); 3.92 (2 H, s,  $CH_2NH_2$ ); 3.09 (4H, q,  $J$  = 7.5 Hz, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.29 (2H, quintet,  $J$  = 7.5 Hz, indane C(2)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 4.04 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 398 (MH-NH<sub>3</sub>)<sup>+</sup>.

10

### Example 71

**1-(2-Amino-5-(aminomethyl)benzoyl-D-phenylglycyl) 4-hydroxypiperidine dihydrochloride salt**

15 **D-Phenylglycine 4-hydroxypiperidinamide trifluoroacetate salt**

A solution of 4-hydroxypiperidine (330 mg, 1.4 mmol) in dimethylformamide (10 mL) was treated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (450 mg; 1.4 mmol) and *N*-ethyldiisopropylamine (0.74 mL, 4.2 mmol). After stirring for 10 minutes, *N*-butoxycarbonyl-D-phenylglycine (330 mg, 1.4 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and water (25 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (5 mL) and stirred for one hour before the solvents were removed under reduced pressure, giving D-phenylglycine-4-hydroxypiperidinamide as its trifluoracetate

salt (150 mg, 43 %).

LC/MS (Luna 2, Gradient 4): rt = 2.64 min, 235 (MH)<sup>+</sup>.

**2-amino-5-cyanobenzoyl-D-phenylglycine 4-**

**5 hydroxypiperidinamide**

A solution of 2-amino-5-cyanobenzoic acid (170 mg, 1.0 mmol) in dimethylformamide (10 mL) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (210 mg, 1.1 mmol) and 1-hydroxy-7-azabenzotriazole (150 mg, 1.1 mmol).

After stirring for 10 minutes, D-phenylglycine 4-hydroxypiperidinamide trifluoroacetate salt (250 mg; 1.1 mmol) was added and the resulting solution stirred overnight at room temperature. The mixture was partitioned between ethyl acetate (25 mL) and water (25 mL) and the organic solution was washed with saturated aqueous citric acid (25 mL), saturated aqueous NaHCO<sub>3</sub> (25 mL) and water (25 mL), dried (MgSO<sub>4</sub>) and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate) to yield 2-amino-5-cyanobenzoyl-D-phenylglycine 4-hydroxypiperidinamide (90 mg, 23 %).

**1-(2-amino-5-(aminomethyl)benzoyl-D-phenylglycyl 4-hydroxypiperidine dihydrochloride salt**

A solution of the nitrile in methanol (10 mL) and 36% hydrochloric acid (0.5 mL) was stirred over 10 % palladium on carbon (20 mg) under an atmosphere of hydrogen for 16 hours. The mixture was filtered and the residue washed with methanol (10 mL) before concentrating the filtrate under reduced pressure. Purification by preparative HPLC afforded 2-amino-5-(aminomethyl)benzoyl-D-phenylglycine 4-hydroxypiperidinamide dihydrochloride salt (30 mg, 33 %).

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 7.84 ppm (1 H, s, Ar); 7.61-7.17 (7 H, m,

Ar); 6.85 (1 H, d,  $J$  = 8 Hz, Ar); 6.12 (1 H, s, CHPh); 4.26 (1 H, m, piperidine C(4)H); 3.99 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 3.79 (2 H, m, piperidine C(2)H and C(6)H); 3.42-3.08 (2H, m, piperidine C(2)H and C(6)H); 1.86-0.72 (4H, m, piperidine C(3)H<sub>2</sub> and C(5)H<sub>2</sub>).

HPLC (Luna 2, Gradient 1): rt = 2.49 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.35 minutes, 366 (MH-NH<sub>3</sub>)<sup>+</sup>.

### Examples 72 and 73

The compounds of Examples 72 and 73 were prepared by the method described below, but using the appropriate starting materials.

Boc D-phenylglycine (251 mg, 1 mmol.) was dissolved in dimethylformamide (3ml) with HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (380 mg., 1 mmol.) and diisopropylethylamine (350 $\mu$ l., 2 mmol.). To this mixture was added 4-methylbenzylamine (121mg., 1 mmol.) and diisopropylethylamine (170 $\mu$ l., 1 mmol.). The mixture was stirred overnight. The mixture was then taken up into ethylacetate and washed with water, sodium carbonate solution, water, 10% hydrochloric acid solution and water. The ethylacetate was evaporated without drying and treated immediately with trifluoroacetic acid (TFA) for 30 min. The TFA was then evaporated to dryness and the product triturated with diethylether. Triethylamine (1ml) was added and evaporated to dryness. A solution of 3-hydroxymethylbenzoic acid (76mg, 0.5mmole) in dry dimethylformamide (DMF) was treated with TBTU (161mg., 0.5mmol.) and diisopropylethylamine (1.5 mmol.). The mixture was then added to the D-phenylglycine-4-methylbenzylamide (0.5mmol.) and stirred overnight. The crude product was

dissolved in water/acetonitrile (20ml), filtered and purified by preparative Hplc to yield pure product.

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.75 (1H, m); 7.65 (2H, m); 7.30 (7H, broad m); 6.80 (3H, m); 5.40 (1H, s); 4.45 (2H, s); 4.10 (2H, m); 5 2.10 (3H, s). MS TOF 389 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 13.51 min.

Compounds made by the above method:-

10 **Example 72.**

**3-Aminomethylbenzoyl-D-phenylglycine-4-aminomethylcyclohexyl methylamide**

<sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.95 (2H, m); 7.80 (2H, m); 7.50 (5H, m); 5.65 (1H, s); 4.45 (2H, s); 3.30 (2H, m); 3.00 (2H, m); 2.00-1.00 15 (10H, m). MS TOF 409 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 3, water/acetonitrile/TFA) rt 12.68 min.

**Example 73.**

**3-Aminomethylbenzoyl-D-phenylglycine-1-adamantylamide**

20 <sup>1</sup>H nmr (CD<sub>3</sub>CN) 7.95 (1H, s); 7.85 (2H, d); 7.60 (1H, m); 7.50 (2H, m); 7.40 (3H, m); 5.65 (1H, s); 4.20 (2H, s); 2.50-1.50 (15H, m). MS TOF 418 (M+1<sup>+</sup>). Hplc (Magellan C8, Gradient 1, water/acetonitrile/TFA) rt 18.36 min.

25 **Example 74**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-(2-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.**

Prepared in a similar manner to Example 35, using (2-hydroxyphenyl)acetic acid.

<sup>1</sup>H NMR (CD<sub>3</sub>CN): 8.91 ppm (1 H, s, OH), 8.30 (1 H, s, NH), 7.94 (2 H, br s, Ar), 7.73 (1 H, d, J = 10 Hz, Ar), 7.54-

7.06 (12 H, m, Ar & NH), 7.01 (1 H, d,  $J = 8$  Hz, Ar), 6.74 (2 H, m, Ar), 5.61 (1 H, d,  $J = 8$  Hz, ArCH<sub>2</sub>), 4.21 (2 H, t,  $J = 8$  Hz, dihydroindole C(2)H<sub>2</sub>), 4.10 (2 H, s, ArCH<sub>2</sub>N), 3.73 (2H, s, ArCH<sub>2</sub>CO), 3.10 (2 H, d,  $J = 8$  Hz, dihydroindole C(3)H<sub>2</sub>).

HPLC (Symmetry, Gradient 2): rt = 6.24 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.10 minutes, 535 (MH)<sup>+</sup>.

#### Example 75

10 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(3-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.**

Prepared in a similar manner to Example 35, using (3-hydroxyphenyl)acetic acid.

15 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.21 ppm (1 H, s, Ar), 7.71 (2 H, br s, Ar), 7.50-7.16 (8 H, m, Ar), 7.05-6.95 (2 H, m, Ar), 6.64-6.50 (3 H, m, Ar), 5.62 (1 H, s, ArCH<sub>2</sub>), 4.09 (2 H, s, ArCH<sub>2</sub>N), 4.04 (2 H, t,  $J = 8$  Hz, dihydroindole C(2)H<sub>2</sub>), 3.68 (2H, s, ArCH<sub>2</sub>CO), 2.91 (2 H, d,  $J = 8$  Hz, dihydroindole C(3)H<sub>2</sub>).

HPLC (Symmetry, Gradient 2): rt = 5.95 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.05 minutes, 535 (MH<sup>+</sup>).

#### Example 76

25 **3-(Aminomethyl)benzoyl-D-phenylglycine 1-(4-hydroxyphenyl)acetyl-2,3-dihydroindol-6-amide trifluoroacetate salt.**

Prepared in a similar manner to Example 35, using (4-hydroxyphenyl)acetic acid.

30 <sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.32 ppm (1 H, s, Ar), 8.04 (2 H, br s, Ar), 7.66-7.34 (8 H, m, Ar), 7.22-7.11 (3 H, m, Ar), 6.80 (2 H, d,  $J = 10$  Hz, Ar), 5.85 (1 H, s, ArCH<sub>2</sub>), 4.21 (2 H, s,

$\text{ArCH}_2\text{N}$ ) , 4.15 (2 H, t,  $J$  = 8 Hz, dihydroindole  $\text{C}(2)\text{H}_2$ ) , 3.81 (2 H, s,  $\text{ArCH}_2\text{CO}$ ) , 3.20 (2 H, d,  $J$  = 8 Hz, dihydroindole  $\text{C}(3)\text{H}_2$ ) .

HPLC (Symmetry, Gradient 2):  $rt$  = 5.97 minutes.

5 LC/MS (Luna 2, Gradient 4):  $rt$  = 2.02 minutes, 535 ( $\text{MH}^+$ ) .

**Example 77**

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-acetylindol-5-amide trifluoroacetate salt.**

10 Prepared in a similar fashion to Example 1, starting from 3-acetyl-5-amino-1-benzylindole, which was prepared as described below.

**3-Acetyl-5-nitroindole and 3-acetyl-7-nitroindole**

15 Prepared by the method described by Ottoni, Cruz and Kramer in *Tetrahedron Letters*, **40**, 1999, 1117-1120, as a mixture of isomers.

20 **3-Acetyl-1-benzyl-5-nitroindole and 3-acetyl-1-benzyl-7-nitroindole**

Potassium carbonate (940 mg, 6.8 mmol) was added to a stirred solution of the above indoles (695 mg, 3.4 mmol) in 25 dimethylformamide (30 mL). Benzyl bromide (0.61 mL, 5.1 mmol) was then added dropwise and the mixture left to stir over the weekend. The dimethylformamide was removed under reduced pressure and the residue partitioned between ethyl acetate (30 mL) and water (20 mL). The ethyl acetate layer 30 was dried ( $\text{MgSO}_4$ ) and evaporated to give the benzylamines as a golden oil.

**3-Acetyl-5-amino-1-benzylindole and 3-acetyl-7-amino-1-benzylindole**

A mixture of the indoles (1.0 g, 3.4 mmol), tin(II) chloride dihydrate (3.48 g, 15.4 mmol) and ethanol (20 mL) was heated at reflux, under an atmosphere of nitrogen, for 3 hours. The mixture was cooled and the solvent evaporated to give a brown oil. To this was added water (50 mL), which was then made basic with 1 N aqueous sodium hydroxide. The aqueous solution was then extracted with ethyl acetate (2 x 30 mL). The whole biphasic mixture was filtered through celite to remove tin salts, separated and the organic solvent dried ( $MgSO_4$ ). The solvent was removed under reduced pressure to give a brown oil which was purified by flash chromatography on silica gel (hexane / ethyl acetate; 3:1) to afford, in order of elution,

**3-acetyl-7-amino-1-benzylindole**

$^1H$  NMR ( $CDCl_3$ ): 7.67 ppm (1 H, s, indole C(2)H); 7.39 - 7.13 (3 H, m, Ph); 7.15 (2 H, m, Ph); 7.05 (1 H, t,  $J$  = 6 Hz, indole C(5)H); 6.57 (1 H, d,  $J$  = 6.5 Hz, indole C(4)H); 6.41 (1 H, d,  $J$  = 6 Hz, indole C(6)H); 5.95 (2 H, br s,  $NH_2$ ); 5.27 (2 H, s,  $PhCH_2$ ); 2.50 (3 H, s,  $CH_3$ )

and **3-acetyl-5-amino-1-benzylindole**

$^1H$  NMR ( $CDCl_3$ ): 8.08 ppm (1 H, d,  $J$  = 6 Hz, indole C(7)H); 7.50 (1 H, s, indole C(2)H); 7.31 - 7.22 (3 H, m, Ph); 7.05 (2 H, m, Ph); 6.63 (1 H, dd,  $J$  = 6, 2 Hz, indole C(6)H); 6.45 (1 H, s, indole 4-H); 5.25 (2 H, s,  $PhCH_2$ ); 3.62 (2 H, br s,  $NH_2$ ); 2.5 (3 H, s,  $CH_3$ ).

**3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-**

**acetylindol-5-amide trifluoroacetate salt.**

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.28 ppm (1 H, s, Ar); 8.20 (1 H, d, J = 5 Hz, Ar); 7.97 (3 H, m, Ar); 7.71 - 7.56 (4 H, m, Ar); 7.47 - 7.19 (9 H, m, Ar); 5.85 (1 H, s, CHPh); 5.45 (2 H, s, 5 CH<sub>2</sub>Ph); 4.21 (2 H, CH<sub>2</sub>NH<sub>2</sub>); 2.53 (3 H, s, CH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 4.15 minutes.

HPLC (Symmetry, Gradient 2): rt = 6.77 minutes.

10 LC/MS (Luna 2, Gradient 4): rt = 2.48 minutes, 531 (MH)<sup>+</sup>.

**Example 78****3-(Aminomethyl)benzoyl-D-phenylglycine 1-benzyl-3-acetylindol-7-amide trifluoroacetate salt.**

15 Prepared in a similar fashion to Example 1, starting from 3-acetyl-7-amino-1-benzylindole, which was prepared as described above.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.46 ppm (1 H, s, Ar); 8.34 (1 H, d, J = 6 Hz, Ar); 8.11 - 7.95 (3 H, m, Ar); 7.75 - 7.48 (4 H, m, Ar); 20 7.46 - 7.12 (9 H, m, Ar); 5.85 (1 H, s, CHPh); 5.48 (2 H, s, CH<sub>2</sub>Ph); 4.21 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.62 (3 H, s, CH<sub>3</sub>) .

HPLC (Luna 2, Gradient 1): rt = 4.58 minutes.

HPLC (Symmetry, Gradient 2): rt = 6.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 2.80 minutes, 531 (MH)<sup>+</sup>.

25

**Example 79****3-(Aminomethyl)benzoyl-D-(4-hydroxyphenyl)glycine indan-5-amide trifluoroacetate salt.**

Prepared in a similar fashion to Example 61, using (4-hydroxyphenyl)glycine and protecting as appropriate.

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 8.00 ppm (2 H, s, Ar); 7.72 - 7.55 (2 H, m, Ar); 7.47 (3 H, t, J = 8.6 Hz, Ar); 7.31 (1 H, d, J = 7.5

Hz, Ar); 7.18 (1 H, d, J = 8 Hz, Ar); 6.86 (2 H, d, J = 8.6 Hz, Ar); 5.75 (1 H, s, CHPh); 4.23 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.94 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.12 (2 H, m, indane C(2)H<sub>2</sub>).

5 HPLC (Luna 2, Gradient 1): rt = 3.78 minutes.

HPLC (Symmetry, Gradient 2): rt = 5.80 minutes.

LC/MS (Luna 2, Gradient 4): rt = 1.83 minutes, 416 (MH)<sup>+</sup>.

**Example 80**

10 **3-(Aminomethyl)benzoyl-D/L-2-(N-formylamino)thiazol-4-yl]glycine 5-indanamide trifluoroacetate salt**

Prepared using the same method as described for Example 61 from D/L- $\alpha$ - (N-<sup>t</sup>butyloxycarbonyl)-[2-(N-formylamino)thiaz-4-yl]glycine (synthesised as described below).

15

**Ethyl  $\alpha$ -azido-[2-(N-formylamino)thiaz-4-yl]acetate**

A solution of ethyl [2-(N-formylamino)thiaz-4-yl]acetate (1 g, 0.0047 mol) in THF (10 mL) was stirred under argon at -78°C and potassium bis(trimethylsilyl)amide (2.8 g, 0.014 mol) in THF (10 mL) was added. After stirring for 30 minutes, 2,4,6-triisopropylbenzenesulfonyl azide (3.6 g, 0.012 mol) was added as a solid in one portion. After 5 minutes, acetic acid (1.4 mL, 0.018 mol) was added and the mixture warmed to room temperature. The reaction mixture was then partitioned between ethyl acetate (100 mL) and water (100 mL), separated and the organic layer dried (MgSO<sub>4</sub>). Evaporation of the solvent and purification of the residue by silica gel chromatography afforded the azide (0.95 g, 80 %).

30 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.78 ppm (1 H, s, NHCHO); 6.98 (1 H, s, C(5)H); 5.95 (1 H, s, CHN<sub>3</sub>); 4.18 (2 H, m, CH<sub>2</sub>CH<sub>3</sub>); 1.20 (3 H, m, CH<sub>2</sub>CH<sub>3</sub>).

**Ethyl α-(N-<sup>t</sup>butyloxycarbonylamino)-[2-(N-formylamino)thiaz-4-yl]acetate**

Di-<sup>t</sup>butyl dicarbonate (0.9 g, 0.004 mol) and 5% palladium on

5 carbon (catalytic amount) were added to a solution of the azide (0.95 g, 0.0037 mol) in methanol (25 mL). The mixture was stirred at room temperature under an atmosphere of hydrogen for 8 hours. After this time the mixture was filtered through celite, washing through with methanol (25 mL). Evaporation of the solvent and purification of the residue by silica gel chromatography afforded the <sup>t</sup>butyloxycarbonyl amine as a pale oily solid (1.1 g, 90 %) <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.53 ppm (1 H, s, NHCHO); 6.89 (1 H, s, C(5)H); 6.18 (1 H, d, J = 8 Hz, NHBoc); 5.38 (1 H, d, J = 8 Hz, CHN); 4.06 (2 H, m, CH<sub>2</sub>CH<sub>3</sub>); 1.28 (9 H, s, tBu); 1.12 (3 H, m, CH<sub>2</sub>CH<sub>3</sub>).

**D/L-α-N-<sup>t</sup>butyloxycarbonyl-[2-(N-formylamino)thiaz-4-yl]glycine**

20 A solution of the ester (1.1 g, 0.0031 g) in THF (25 mL) was treated with 1 M aqueous LiOH (5 ml, 0.005 mol) and heated at reflux for 1 hour. The solvent was removed under reduced pressure and the residue diluted with water (100 mL). The pH was reduced to 2 using 5% aqueous HCl and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated under reduced pressure to afford the acid as a white solid (0.8 g, 84 %).

<sup>1</sup>H NMR (d<sub>4</sub> MeOH): 8.38 ppm (1 H, s, NHCHO); 7.01 (1 H, s,

30 C(5)H); 5.21 (1 H, s, CHN); 1.39 (9 H, s, <sup>t</sup>Bu).

**3-(Aminomethyl)benzoyl-D/L-[2-(formylamino)thiazol-4-**

**4-ylglycine 5-indanamide trifluoroacetate salt**

<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 10.10 ppm (1 H, s, NHCHO); 8.80 (1 H, d, J = 8 Hz, NH); 8.48 (1 H, s, NHCHO); 7.97 (2 H, br s, Ar); 7.58 (2 H, m, Ar); 7.42 (1 H, s, aminothiazole C(5)H); 7.37 (1 H, d, J = 7 Hz, indane C(6)H); 7.18 (1 H, s, indane C(4)H); 7.10 (1 H, d, J = 7Hz, indane C(7)H); 5.92 (1 H, m, CHAr); 4.18 (2 H,s, CH<sub>2</sub>NH<sub>2</sub>); 2.83 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.02 (2 H, m, indane C(2)H<sub>2</sub>)  
HPLC (Luna 2, gradient 1): rt = 3.71 minutes.  
LC/MS (Luna 2, gradient 4): rt = 2.05 minutes; 450 (MH)<sup>+</sup>.

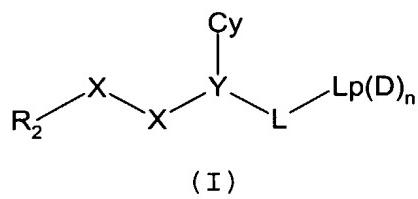
**Example 81****3-(Aminomethyl)benzoyl-D/L-2-aminothiazol-4-ylglycine-5-indanamide bis(hydrochloride) salt.**

Prepared from D/L- $\alpha$ -N-<sup>t</sup>butyloxycarbonyl-[2-(N-formylamino)thiaz-4-yl]glycine and synthesised using the method of Example 80 except that the final deprotection was effected using 3 M aqueous HCl in THF, in order to remove both the <sup>t</sup>butyloxycarbonyl and formyl protecting groups.  
<sup>1</sup>H NMR (d<sub>4</sub> MeOH) : 7.87 ppm (2 H, m, Ar); 7.51 (1 H, m, Ar); 7.48 (1 H, t, J = 7 Hz, (aminomethyl)benzoyl C(3)H); 7.40 (1 H, s, aminothiazole C(5)H); 7.20 (1 H, d, J = 8 Hz, indane C(6)H); 7.05 (1 H, d, J = 8 Hz, indane C(7)H); 6.73 (1 H, s, indane C(4)H); 5.78 (1 H, s, CHAr); 4.12 (2 H, s, CH<sub>2</sub>NH<sub>2</sub>); 2.79 (4 H, m, indane C(1)H<sub>2</sub> and C(3)H<sub>2</sub>); 2.00 (2 H, m, indane C(2)H<sub>2</sub>).  
HPLC (Luna 2, gradient 1): rt = 3.21 minutes.  
LC/MS (Luna 2, gradient 4): rt = 1.78 minutes; 422 (MH)<sup>+</sup>.  
The compounds of formula (I) exemplified in the Examples - Part 2 have been found to be inhibitors of tryptase by the method of Tapparelli et al (J. Biol. Chem. 1993, 268, 4734-

4741) .

## CLAIMS

1. A method of treatment of the human or non-human animal body to combat a condition responsive to a serine protease inhibitor, said method comprising administering to said body an effective amount of a serine protease inhibitor compound of formula (I)



10 where  $\text{R}_2$  represents a 5 or 6 membered aromatic carbon ring optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, 15 alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy,  $\text{MeSO}_2^-$  or  $\text{R}_1$ , or the substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo, haloalkoxy, haloalkyl, cyano, nitro, 20 amino, hydrazido, alkylthio, alkenyl, alkynyl or  $\text{R}_{1j}$ , and optionally substituted in the position alpha to the X-X group by amino, hydroxy, halo, alkyl, carboxy, alkoxycarbonyl, cyano, amido, aminoalkyl, hydroxyalkyl, alkoxy or alkylthio with the proviso that  $\text{R}_2$  cannot be 25 aminoisoquinolyl;

each X independently is a C, N, O or S atom or a CO,  $\text{CR}_{1a}$ ,  $\text{C}(\text{R}_{1a})_2$  or  $\text{NR}_{1a}$  group, at least one X being C, CO,  $\text{CR}_{1a}$  or  $\text{C}(\text{R}_{1a})_2$ ;

each  $\text{R}_{1a}$  independently represents hydrogen or hydroxyl, 30 alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl,

alkoxycarbonyl, alkylaminocarbonyl, alkoxycarbonylamino, acyloxymethoxycarbonyl or alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl;

5 L is an organic linker group containing 1 to 5 backbone atoms selected from C, N, O and S, or a branched alkyl or cyclic group;

Y (the  $\alpha$ -atom) is a nitrogen atom or a CR<sub>1b</sub> group;

Cy is a saturated or unsaturated, mono or poly cyclic, homo or heterocyclic group, optionally substituted by groups 10 R<sub>3a</sub> or phenyl optionally substituted by R<sub>3a</sub>:

each R<sub>3a</sub> independently is R<sub>1c</sub>, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl thiazolyl, alkyl oxazolyl, 15 oxazolyl, alkylsulphonamido, alkylaminosulphonyl, aminosulphonyl, haloalkoxy and haloalkyl;

Lp is a lipophilic organic group;

D is a hydrogen bond donor group; and n is 0, 1 or 2; and

20 R<sub>1</sub>, R<sub>1b</sub>, R<sub>1c</sub> and R<sub>1j</sub> are as defined for R<sub>1a</sub>, or a physiologically tolerable salt thereof.

2. A method as claimed in Claim 1, where

R<sub>2</sub> represents a 5 or 6 membered aromatic carbon ring 25 optionally interrupted by a nitrogen, oxygen or sulphur ring atom, optionally being substituted in the 3 and/or 4 position by halo, nitro, haloalkoxy, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, or the 30 substituents at the 3 and 4 positions taken together form a fused ring which is a 5 or 6 membered carbocyclic or heterocyclic ring optionally substituted by halo,

haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>, and optionally substituted in the position alpha to the X-X group by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, 5 alkoxy or alkylthio with the proviso that R<sub>2</sub> cannot be isoquinolyl; and

each R<sub>1a</sub> independently represents hydrogen or hydroxyl, alkoxy, alkyl, aminoalkyl, hydroxyalkyl alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl or 10 alkylamino optionally substituted by hydroxy, alkylamino, alkoxy, oxo, aryl or cycloalkyl.

3. A method as claimed in Claim 1 or Claim 2, in which n is 0.

15

4. A method as claimed in any one of Claims 1 to 3, in which X-X is selected from -CH=CH-, -CONH-, -CONR<sub>1a</sub>-, -NH-CO-, -NH-CH<sub>2</sub>-, -CH<sub>2</sub>-NH-, -CH<sub>2</sub>O-, -OCH<sub>2</sub>-, -COO-, -OC=O- and -CH<sub>2</sub>CH<sub>2</sub>- is CONH.

20

5. A method as claimed in Claim 4, in which X-X is CONH.

25

6. A method as claimed in any one of Claims 1 to 5, in which Y is a CR<sub>1b</sub> group and has the conformation that would result from construction from a D- $\alpha$ -aminoacid NH<sub>2</sub>-CR<sub>1b</sub>(Cy)-COOH where the NH<sub>2</sub> represents part of X-X.

30

7. A method as claimed in any one of Claims 1 to 6, in which Y is CH.

8. A method as claimed in any one of Claims 1 to 7, in which Cy represents an optionally R<sub>3a</sub> substituted phenyl,

pyridyl, thienyl, thiazolyl, naphthyl, piperidinyl or cycloalkyl group.

9. A method as claimed in Claim 8, in which R<sub>3a</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, methylaminomethyl, dimethylaminomethyl, hydroxymethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, CONH<sub>2</sub>, CH<sub>2</sub>CONH<sub>2</sub>, aminoacetyl, formylamino, acetylamino, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, methylsulphenyl, imidazol-4-yl, hydrazido, 2-methylimidazol-4-yl, methylsulphonylamido, ethylsulphonylamido, 15 methylaminosulphonyl, ethylaminosulphonyl, aminosulphonyl, trifluoromethoxy and trifluoromethyl.

10. A method as claimed in any one of Claims 1 to 9, in which Cy is phenyl, 4-aminophenyl, 4-amidophenyl, 4-(N-methyl)amidophenyl, 4-(N,N-dimethyl)amidophenyl, 2-chlorophenyl, 2-methylphenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-aminomethylphenyl, 4-aminomethylphenyl, 2-hydroxymethylphenyl, 3-hydroxymethylphenyl, 4-hydroxymethylphenyl, 4-carboxyphenyl, 3-ethylsulphonylaminophenyl, thien-2-yl, thien-3-yl, thiazol-4-yl, thiazol-5-yl, 2-methylthiazol-4-yl, 2-aminothiazol-4-yl, 2-formylaminothiazol-4-yl, 2-aminothiazol-5-yl, 2-formylaminothiazol-5-yl, pyrid-2-yl, 25 pyrid-3-yl, pyrid-4-yl, 4-aminopyrid-3-yl, 4-aminopyrid-4-yl, piperidin-4-yl, 1-methylpiperidin-4-yl, cyclohexyl or naphth-1-yl.

11. A method as claimed in any one of Claims 1 to 10, in which L represents CO, CH<sub>2</sub>NH, CONR<sub>1d</sub>(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m</sub>N(R<sub>1d</sub>)CO(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m+2</sub>, CO(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m</sub>CO, (CH<sub>2</sub>)<sub>m</sub>OC=O, (CH<sub>2</sub>)<sub>m</sub>O, CH=CH(CH<sub>2</sub>)<sub>m</sub>, SO<sub>2</sub>, SO<sub>2</sub>NR<sub>1d</sub>, SO<sub>2</sub>(CH<sub>2</sub>)<sub>m</sub>, (CH<sub>2</sub>)<sub>m</sub>SO<sub>2</sub> or (CH<sub>2</sub>)<sub>m</sub>SO<sub>2</sub>NR<sub>1d</sub> (where each m is independently 0 or 1 and R<sub>1d</sub> is as defined for R<sub>1a</sub>).

12. A method as claimed in Claim 11, in which L is CO, CONH, CH<sub>2</sub>NHCO and CONHCH<sub>2</sub>.

10

13. A method as claimed in any one of Claims 1 to 12, in which R<sub>2</sub> represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by halo, nitro, thiol, haloalkoxy, hydrazido, alkylhydrazido, amino, cyano, haloalkyl, alkylthio, alkenyl, alkynyl, acylamino, tri or difluoromethoxy, carboxy, acyloxy, MeSO<sub>2</sub>- or R<sub>1</sub>, and optionally substituted at the 6 position by amino, hydroxy, halo, alkyl, carboxy, alkoxy carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(ii) naphth-2-yl optionally substituted at the 6 or 7 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub> and optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

(iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by halo, haloalkoxy, haloalkyl, cyano, 5 nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(vi) 3,4-methylenedioxyphenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

10 (vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

15 (ix) pyrid-2-yl optionally substituted at the 5 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

(x) pyrid-3-yl optionally substituted at the 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1</sub>;

20 (xi) benzofur-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

25 (xii) indol-2-yl optionally substituted on the indole nitrogen atom by alkyl and optionally substituted at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>;

30 (xiii) indol-6-yl substituted at the 5 position by amino, hydroxy, halo (such as fluoro or chloro), alkyl, carboxy, alkoxy carbonyl, cyano, amido, aminoalkyl, alkoxy or alkylthio and optionally substituted at the 3 position by

halo (such as chloro), haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>; or

(xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by amino, hydroxy, halo, alkyl, carboxy, 5 cyano, amido, aminoalkyl, alkoxy or alkylthio and at the 5 or 6 position by halo, haloalkoxy, haloalkyl, cyano, nitro, amino, hydrazido, alkylthio, alkenyl, alkynyl or R<sub>1j</sub>.

14. A method as claimed in Claim 13, in which R<sub>2</sub>

10 represents:

(i) phenyl optionally being substituted in the 3 and/or 4 position by fluoro, chloro, bromo, iodo, nitro, difluoromethoxy, trifluoromethoxy, amino, cyano, trifluoromethyl, methylthio, vinyl, carboxy, acetoxy, MeSO<sub>2</sub>- 15 , hydroxy, methoxy, ethoxy, methyl, methoxycarbonyl, methylamino, ethylamino or amido, and optionally substituted at the 6 position by amino, hydroxy, fluoro, methoxycarbonyl, cyano or aminomethyl (preferably phenyl substituted in the 4 position by chloro, amino, vinyl, 20 methylamino, methyl or methoxy, optionally at the 3 position with amino or hydroxy, and optionally at the 6 position with amino or hydroxy);

(ii) naphth-2-yl optionally substituted at the 6, position by hydroxy and optionally substituted at the 3 25 position by amino or hydroxy;

(iii) isoquinolin-7-yl, indol-5-yl, indol-6-yl, indazol-5-yl, indazol-6-yl, benzothiazol-6-yl or benzisoxazol-5-yl optionally substituted at the 3 position by chloro, bromo, amino, methyl or methoxy;

30 (iv) benzimidazol-5-yl or benzothiazol-6-yl optionally substituted at the 2 position by amino;

(v) thien-2-yl or thien-3-yl optionally substituted at the 4 or 5 position by methylthio, methyl or acetyl;

(vi) 3,4-methylenedioxypyhenyl, 2,3-dihydroindol-6-yl, 3,3-dichloro-2-oxo-indol-6-yl or 1-methyl-3-aminoindazol-5-yl;

(vii) benzothiazol-2-yl, imidazo[1,2-a]pyrimidin-2-yl or tetrahydroimidazo[1,2-a]pyrimidin-2-yl;

(viii) pyrazol-2-yl substituted at the 5 position by methyl;

10 (ix) pyrid-2-yl optionally substituted at the 6 position by chloro;

(x) pyrid-3-yl optionally substituted at the 4 position by chloro;

15 (xi) benzofur-2-yl optionally substituted at the 3 position by chloro, methyl or methoxy, at the 5 or 6 position by methyl and at the 6 position by methoxy;

(xii) indol-2-yl optionally substituted on the indole nitrogen atom by methyl and optionally substituted at the 5 or 6 position by fluoro, chloro, bromo, methyl or methoxy;

20 (xiii) indol-6-yl substituted at the 5 position by chloro, fluoro or hydroxy and optionally substituted at the 3 position by chloro or methyl; or

25 (xiv) benzo[b]thiophen-2-yl optionally substituted at the 3 position by fluoro, chloro or methyl, and optionally substituted at the 5 or 6 position by fluoro, chloro, methyl, hydroxy, or methoxy.

15. A method as claimed in any one of Claim 14,  
in which R<sub>2</sub> represents indol-6-yl optionally substituted at  
30 the 3 position by chloro, bromo, methyl or methoxy or indol-6-yl substituted at the 5 position by chloro, fluoro or

hydroxy and optionally substituted at the 3 position by chloro or methyl.

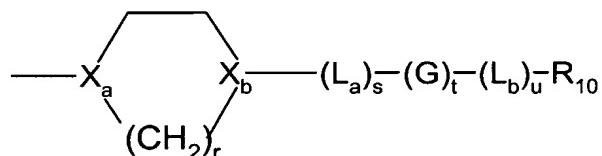
16. A method as claimed in any one of Claims 1 to 15,  
5 in which L<sub>p</sub> is an alkyl, alkenyl, carbocyclic or heterocyclic group, or a combination of two or more such groups linked by a spiro linkage or a single or double bond or by C=O, O, S, SO, SO<sub>2</sub>, CONR<sub>1e</sub>, NR<sub>1e</sub>-CO-, NR<sub>1e</sub> linkage (where R<sub>1e</sub> is as defined for R<sub>1a</sub>), optionally substituted by  
10 one or more oxo or R<sub>3</sub> groups in which R<sub>3</sub> is alkylaminocarbonyl, alkoxy carbonylamino, N-alkylaminoalkanoyl, N-alkanoylaminoalkanoyl, C-hydroxyaminoalkanoyl or as defined for R<sub>3a</sub>.

15 17. A method as claimed in Claim 16, in which R<sub>3</sub> is selected from hydrogen, hydroxyl, methoxy, ethoxy, methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, t-butyl, pentyl, 2-pentyl or 3-pentyl, isopropylaminomethyl, dimethylaminomethyl,  
20 diethylaminomethyl, dimethylaminoethyl, acetyl, hydroxymethyl, hydroxyethyl, carboxy, methoxymethyl, methoxycarbonyl, ethoxycarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, aminomethyl, aminocarbonyl, methylamino, dimethylamino, ethylamino, formylamino, acetylamino, amino, fluoro, chloro, cyano, nitro, thiol, methylthio, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, methylsulphenyl, 1,2,4-triazol-2-yl, 1,2,4-triazol-4-yl, 1,2,3-triazol-4-yl, 1,3-imidazol-1-yl or 1,3-imidazol-4-yl, tetrazol-1-yl, tetrazol-5-yl;  
30 methylsulphonamido, ethylsulphonamido, propylsulphonamido, methylaminosulphonyl, ethylaminosulphonyl,

propylaminosulphonyl, aminosulphonyl, trifluoromethoxy, trifluoromethyl and trichloromethyl.

18. A method as claimed in any one of Claims 1 to 17 in  
5 which said condition is a condition responsive to a Factor  
Xa inhibitor and R<sub>1</sub> is not an unsubstituted aminoalkyl  
group.

19. A method as claimed in Claim 18, in which L<sub>p</sub> is a group  
10 of formula:



in which:

r is 1 or 2;

one of X<sub>a</sub> and X<sub>b</sub> is N and the other is CH or N provided that  
15 when r is 1, X<sub>a</sub> and X<sub>b</sub> are not both N;

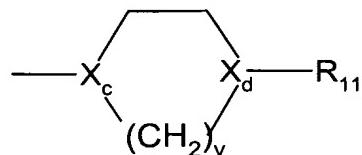
s, t and u are each 0 or 1;

L<sub>a</sub> and L<sub>b</sub> are each independently selected from a single  
bond, C=O, O and NR<sub>1e</sub>, in which R<sub>1e</sub> is hydrogen or (1-  
6C)alkyl;

20 G is (1-6C)alkanediyl; and

R<sub>10</sub> is (1-6C)alkyl, (3-6C)cycloalkyl which is unsubstituted  
or substituted by (1-6C)alkyl, indanyl, pyridyl,  
tetrahydropyran, tetrahydrothiopyran, phenyl which is  
unsubstituted or substituted by one or two R<sub>3</sub> groups,

25 pyrrolinyl, or a group of formula



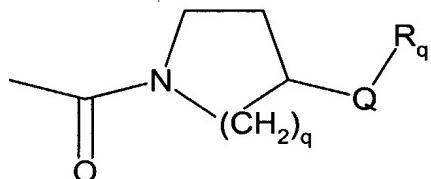
in which v is 1, 2 or 3; one of  $X_C$  and  $X_D$  is N and the other is CH or N, provided that when v is 1,  $X_C$  and  $X_D$  are not both N; and  $R_{11}$  is hydrogen, (1-6C)alkyl or when  $X_D$  is CH, hydroxy(1-6C)alkyl; provided that when t is 0, the sum of s and u is 1; when  $X_B$  is N,  $L_a$  is a bond or C=O; when  $X_C$  is N,  $L_b$  is a bond or C=O; when  $X_B$  and  $X_C$  are both N, t is 1; and when  $(L_a)_s - (G)_t - (L_b)$  represents an alkyl group and  $X_B$  and  $X_C$  both represent N, the alkyl group contains at least two chain carbon atoms.

10

20. A method as claimed in Claim 19, in which either  $X_a$  is N and L is CO or  $CH_2CO$ , or  $X_a$  is CH and L is CONH, CONH $CH_2$  or  $CH_2NHCO$ .

15 21. A method as claimed in Claim 18, in which  
-L-Lp(D)<sub>n</sub> is:

(i)



in which q is 1 or 2;

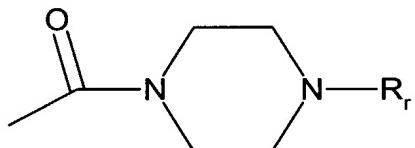
20 (a) Q is a direct bond; and R<sub>q</sub> is piperidin-4-yl which may bear a C<sub>1-3</sub>alkyl substituent at the 1-position; or R<sub>q</sub> is NR<sub>a</sub>R<sub>b</sub> in which each of R<sub>a</sub> and R<sub>b</sub> independently is hydrogen or C<sub>1-3</sub>alkyl; or one of R<sub>a</sub> and R<sub>b</sub> is hydrogen or methyl and the other of R<sub>a</sub> and R<sub>b</sub> is -CH<sub>2</sub>-R<sub>c</sub> or -CH<sub>2</sub>-R<sub>d</sub> in which R<sub>c</sub> is pyridyl or phenyl (which phenyl may bear a fluoro, chloro, methyl, CONH<sub>2</sub>, SO<sub>2</sub>NH<sub>2</sub>, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonylamino, methoxy or methylsulphonyl substituent) and in which R<sub>d</sub> is isopropyl or

cyclopentyl, or  $\text{NR}_a\text{R}_b$  is pyrrolidino, piperidino, morpholino, piperazino, or tetrahydro-1,4-diazepino in which a pyrrolidino or piperidino may be a 3,4-didehydro derivative and in which a pyrrolidino, piperidino, 5 piperazino, or tetrahydro-1,4-diazepino may bear a methyl group at the 4-position;

(b) Q is -O- or -NH-; and  $\text{R}_Q$  is  $\text{R}_C$  which is defined as above; or

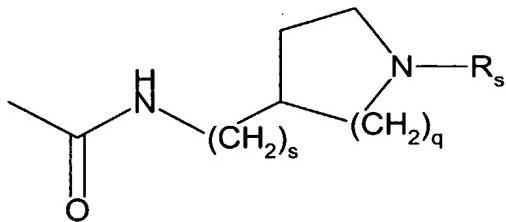
10 (c) Q is methylene; and  $\text{R}_Q$  is  $\text{NR}_a\text{R}_b$  which is defined as above;

(ii)



in which  $\text{R}_r$  is  $-(\text{CH}_2)_c\text{R}_C$ ,  $-\text{CHR}_e\text{R}_f$ ,  $-\text{CH}_2-\text{CHR}_e\text{R}_f$ , or  $\text{R}_g$  in which c is 1 or 2 and  $\text{R}_C$  is defined as above; each of  $\text{R}_e$  and 15  $\text{R}_f$  independently is hydrogen or  $\text{C}_{1-3}$ alkyl; or  $\text{CHR}_e\text{R}_f$  is cyclopentyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), cyclohexyl (which may bear a methyl, ethyl or hydroxymethyl substituent at the 3- or 4-position), tetrahydropyran-4-yl, tetrahydrothiopyran-4- 20 yl, pyrrolidin-3-yl (which may bear a 1-methyl substituent), piperidin-4-yl (which may bear a 1-methyl substituent), or indan-2-yl; and  $\text{R}_g$  is 2-methylsulphonylphenyl which may bear a 4-fluoro substituent or  $\text{R}_g$  is  $\lambda^{6-1,1-}$  dioxobenzo[b]thiophen-7-yl;

25 (iii)

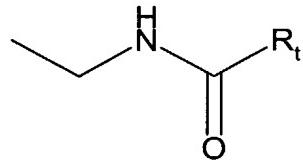


in which q is 1 or 2;

s is 0 or 1; and

Rs is  $-(CH_2)_c-R_C$ ,  $-CHR_eR_f$ , or  $-CH_2-CHR_eR_f$  each of which  
5 is defined as above;

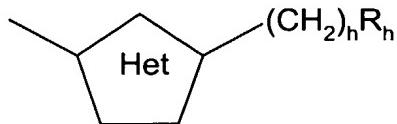
(iv)



in which Rt is piperidin-4-yl, piperidin-3-yl or  
pyrrolindin-3-yl, any of which may bear a C1-3 alkyl

10 substituent at the 1-position (preferably methyl, ethyl or,  
more preferably, 2-propyl); or Rt is phenyl (which phenyl  
may bear a fluoro, chloro, C1-4 alkyl, methoxy or  
methylsulphonyl substituent); or

(v)



15

in which Het is a divalent 5 membered heteroaromatic group  
containing 1, 2 or 3 heteroatoms selected from O, N and S  
and having the two ring atoms at which it is connected  
separated by one ring atom;

20 h is 0 or 1; and

Rh is phenyl which may bear one or more R3  
substituents.

22. A method as claimed in Claim 21, in which

(i) q is 2, and

in (a) R<sub>q</sub> is piperidin-4-yl which may bear a (1-3C)alkyl substituent at the 1-position;

5 and in (b) R<sub>c</sub> is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl);

(ii) c is 2 and R<sub>c</sub> is pyrid-2-yl, pyrid-3-yl or pyrid-4-yl;

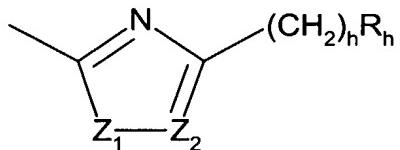
(iii) s is 1;

(iv) R<sub>t</sub> is piperidin-4-yl which may bear a methyl, ethyl or 2-propyl substituent at the 1-position; and

10 (v) R<sub>h</sub> is phenyl which may bear one or more R<sub>3</sub> substituents independently selected from, for an ortho or a para substituent: C<sub>1-5</sub> alkyl, fluoro, chloro, difluoromethyl, trifluoromethyl, methoxy, dimethylamino, methylsulphonyl, and C<sub>1-2</sub> acyl, and for a meta substituent: fluoro, chloro  
15 and methyl.

23. A method as claimed in Claim 18, in which

-L-Lp(D)<sub>n</sub> is



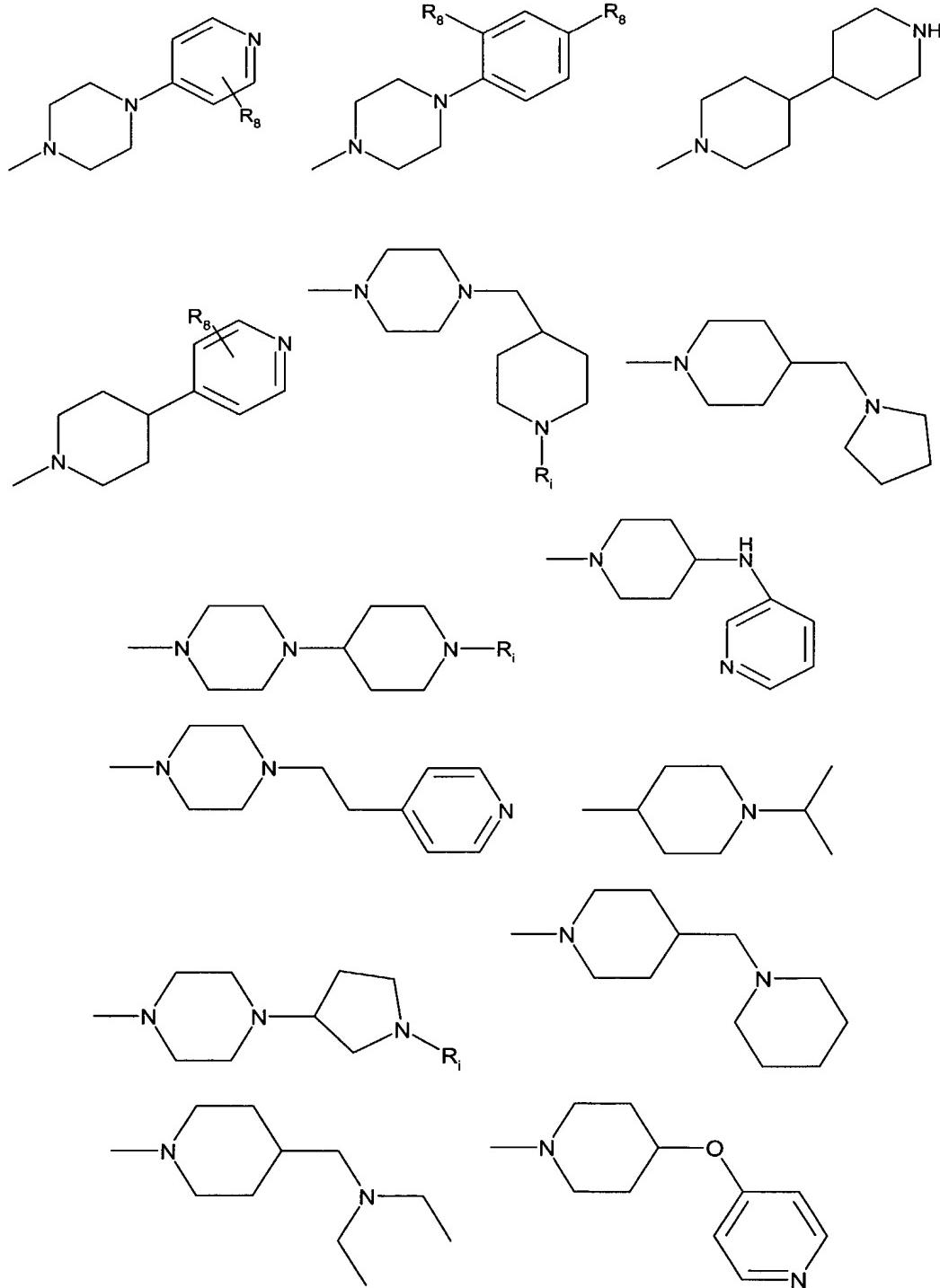
20 in which R<sub>h</sub> is phenyl which may bear an ortho and/or a para substituent independently selected from, for an ortho: methyl, fluoro, chloro, methylsulphonyl and acetyl, and for a para substituent: methyl, fluoro, chloro, methoxy and dimethylamino;

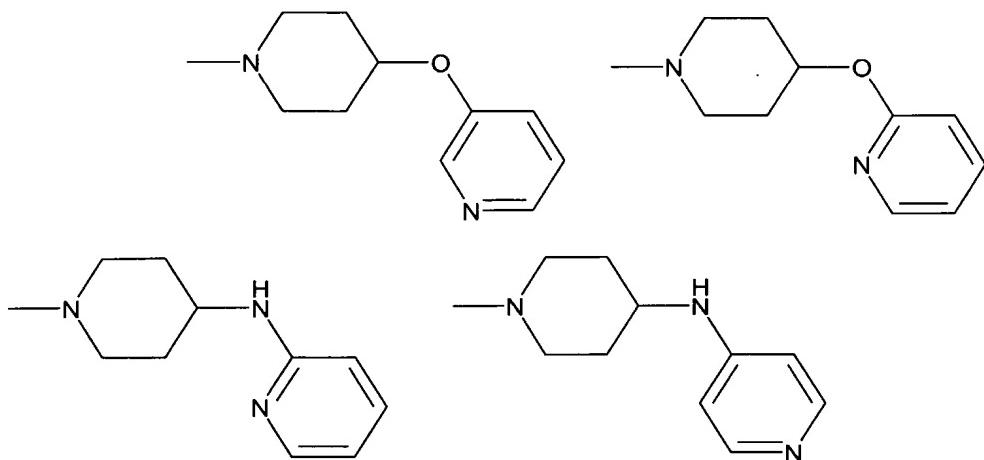
25 Z<sub>1</sub> is S, Z<sub>2</sub> is CH, h is 0; or

Z<sub>1</sub> is NH, Z<sub>2</sub> is N, h is 1.

24. A method as claimed in Claim 18, in which Lp is

selected from

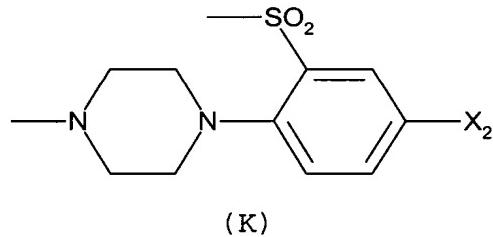




where  $R_8$  represents H, OMe,  $\text{SO}_2\text{Me}$ , F, cyano, amido, amino,  $\text{NO}_2$ , Cl or OH; and  $R_i$  is hydrogen or (1-6C)alkyl.

5

25. A method as claimed in Claim 18, in which  $L_p$  represents



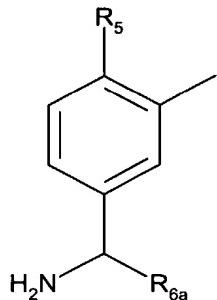
wherein  $X_2$  is halo, hydrogen, amino, nitro or  $\text{CONH}_2$ .

10

26. A method as claimed in any one of Claims 1 to 17, in which said condition is a condition responsive to a tryptase inhibitor and  $R_2$  is substituted in the 3 and/or 4 position by  $R_1$  in which  $R_1$  is an unsubstituted aminoalkyl group.

15

27. A method as claimed in Claim 26, in which  $R_2$  group is of the formula



in which  $R_5$  is amino, hydroxy, aminomethyl, hydroxymethyl or hydrogen, and  $R_{6a}$  is hydrogen or methyl.

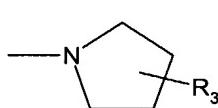
5 28. A method as claimed in Claim 27, in which  $R_2$  is 3-aminomethylphenyl or 3-aminomethyl-6-aminophenyl.

29. A method as claimed in Claim 28, in which  $R_2$  is 3-aminomethylphenyl.

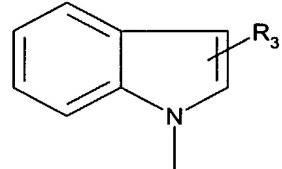
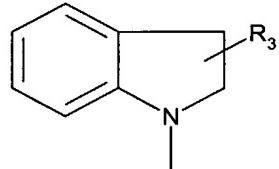
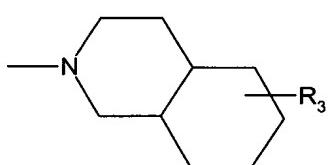
10

30. A method as claimed in any one of Claims 26 to 29, in which:

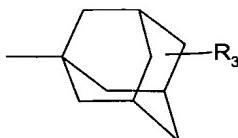
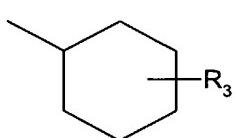
(i) L represents CO and Lp represents

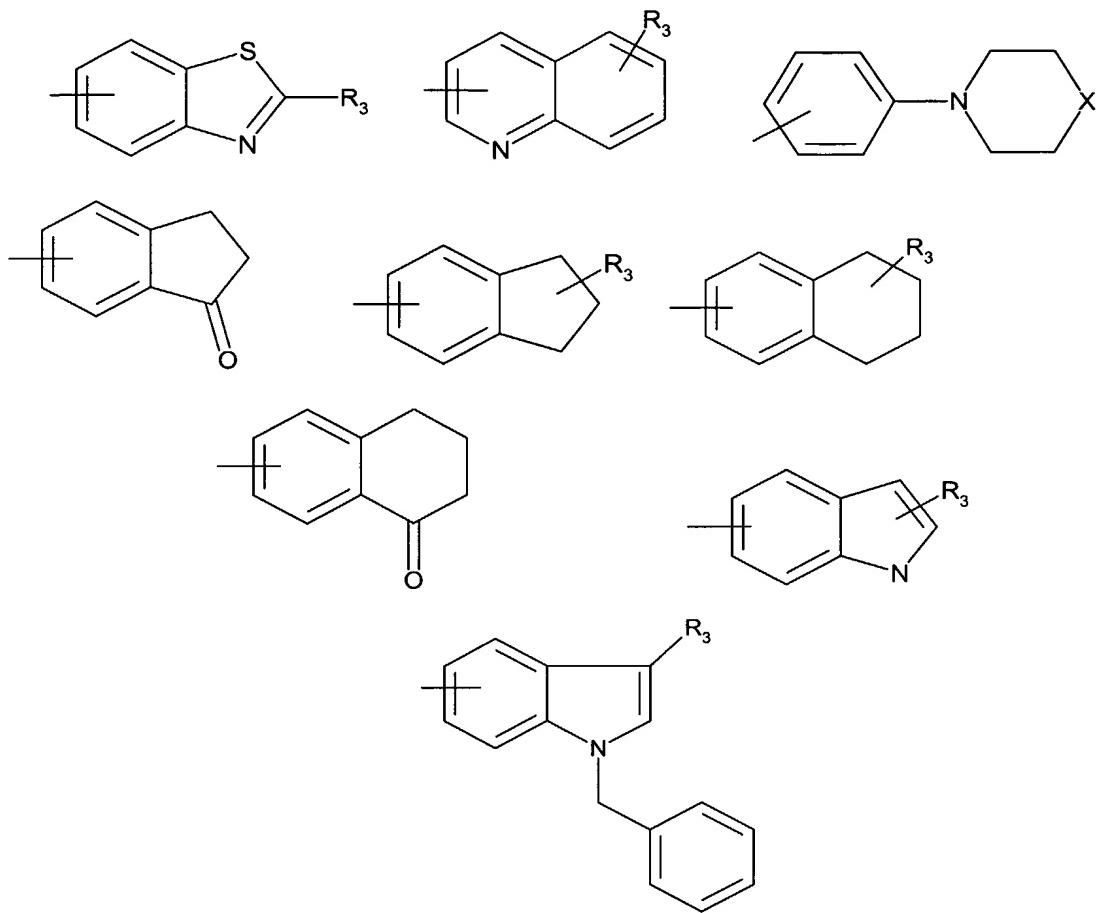


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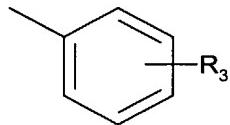
(ii) L represents CONH and Lp represents





5 in which X is CH or N;

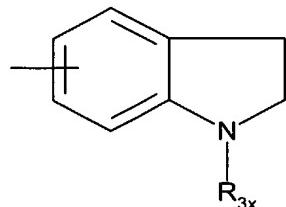
(iii) L represents CONH and Lp represents



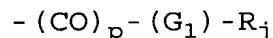
in which R<sub>3</sub> is alkylaminocarbonyl, N-alkylaminoalkanoyl, N-alkanoylaminoalkanoyl, C-hydroxyaminoalkanoyl, hydrogen,  
 10 alkoxy, alkyl, aminoalkyl, aminocarbonyl, hydroxyalkyl, alkoxyalkyl, alkoxycarbonyl, acyloxymethoxycarbonyl, alkylamino, amino, halo, cyano, nitro, thiol, alkylthio, alkylsulphonyl, alkylsulphenyl, triazolyl, imidazolyl, tetrazolyl, hydrazido, alkyl imidazolyl, thiazolyl, alkyl  
 15 thiazolyl, alkyl oxazolyl, oxazolyl, alkylsulphonamido,

alkylaminosulphonyl, aminosulphonyl, haloalkoxy or haloalkyl; or

(iv) L represents CONH and Lp represents



5 in which R<sub>3x</sub> represents R<sub>3</sub> or a group of formula



in which p is 0 or 1; G<sub>1</sub> represents (1-3C) alkanediyl or, when p is 1, a bond; and R<sub>j</sub> represents a carbocyclic or heterocyclic group, optionally substituted by R<sub>3</sub>.

10

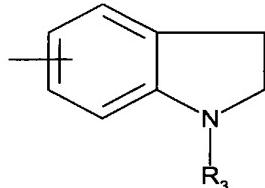
31. A method as claimed in Claim 30, in which:

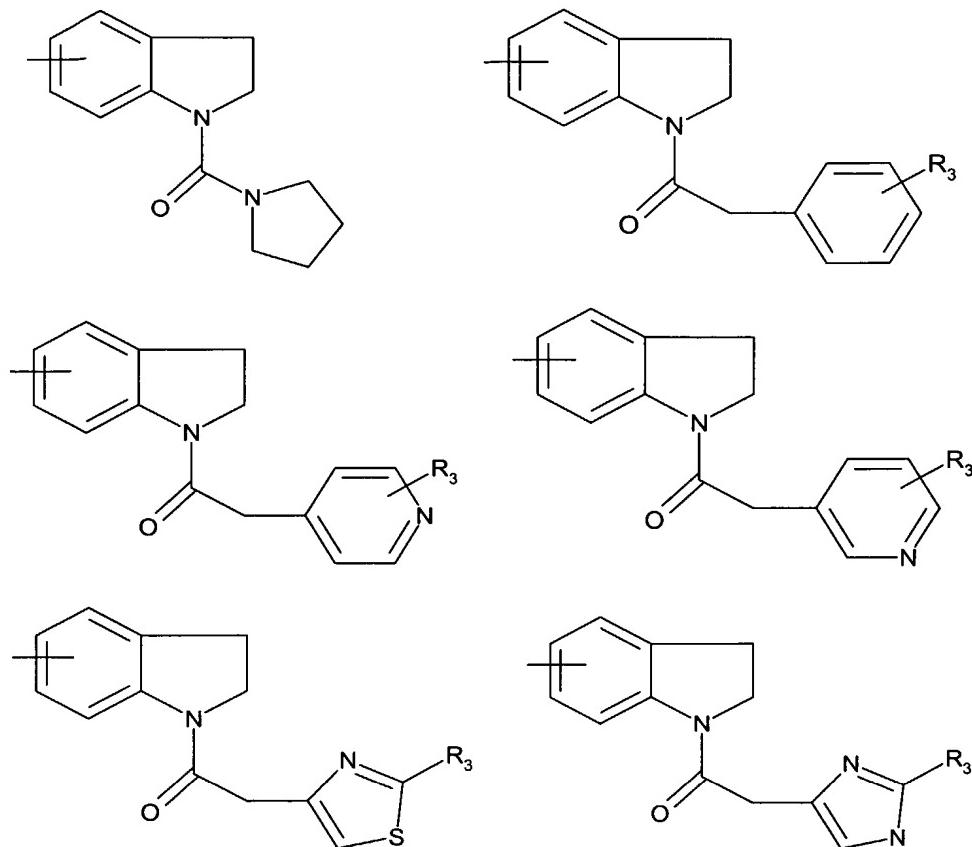
in (i) R<sub>3</sub> represents hydrogen, hydroxyl or alkylaminocarbonyl;

in (ii) R<sub>3</sub> is hydrogen, amino, hydroxy, alkyl or aminoalkyl;

15 in (iii) the phenyl group is unsubstituted or substituted by one or two R<sub>3</sub> groups; and

in (iv) the 2,3-dihydroindolyl group is a 2,3-dihydroindol-5-yl or 2,3-dihydro-6-yl group of the formula





in which: when  $\text{R}_3$  is a substituent on the 1-position of a

5 2,3-dihydroindolyl group, it represents alkylaminocarbonyl; N-alkylaminoalkanoyl; N-alkanoylaminoalkanonyl; C-hydroxyaminoalkanoyl; hydrogen; alkyl; alkanoyl; alkoxycarbonyl; acyloxymethoxycarbonyl; aminoalkyl; aminoalkanoyl; hydroxyalkyl; hydroxyalkanoyl; alkoxyalkyl; or alkanoylamino; and when  $\text{R}_3$  is a substituent on a phenyl, thiazolyl, imidazolyl or pyridyl group, it is hydrogen, amino, alkyl or aminoalkyl.

10 32. Use of a compound as defined in any one of Claims 1 to  
15 31 for the manufacture of a medicament for the treatment of  
a condition as defined in any one of Claims 1 to 31.

33. A pharmaceutical composition for use in the treatment of a condition as defined in any one of Claims 1 to 31, which comprises a compound as defined in any one of Claims 1 to 31.